CENTERS FOR MEDICARE AND MEDICAID SERVICES

Medicare Coverage Advisory Committee

February 12, 2003

Baltimore Convention Center
100 West Pratt Street
Baltimore, Maryland

Panelists

Chairperson
Harold C. Sox, MD

Voting Members
Colleen Conway-Welch, PhD, RN
Anne Curtis, MD, FACC
Carole Flamm, MD
Thomas Holohan, M.D.
Alexander Krist, MD
Karl Matuszewski, PharmD, MS
Rita F. Redberg, MD, MSc, FACC

Consumer Representative
Phyllis E. Greenberger, MSW

Industry Representative
Jonathan Weil, PhD, JD

Panelists (Continued)

Invited Guests
Thomas Bigger, MD
Alfred Buxton, MD
Mark Carlson, MD
Kerry Lee, MD
Bruce Wilkoff, MD

HCFA Liaison
Sean R. Tunis, MD, MSc

Executive Secretary
Janet Anderson

PANEL PROCEEDINGS

(The meeting was called to order at 8:07 a.m., Wednesday, February 12, 2003.

Ms. Anderson: Good morning and welcome, chairperson, members and guests. I am Janet Anderson, Executive Secretary of the Medical Coverage Advisory Committee, MCAC. The committee is here today to hear and discuss evidence and testimony regarding the use of implantable defibrillators. The committee will make recommendations to CMS concerning the quality of the evidence for the use of the implantable defibrillators.

In evaluating the evidence presented to you today, CMS encourages the committee to consider all relevant forms of information, including but not limited to professional society statements, clinical guidelines and other testimony you may hear during the course of this meeting.

The following announcement addresses conflict of interest issues associated with this meeting and is made part of the record to preclude even the appearance of impropriety. The conflict of interest statutes prohibit special government employees from participating in matters that could affect their or their employers financial interests.

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To determine if any conflict existed, the Agency reviewed all financial interests reported by the committee participants. The Agency has determined that all members may participate in the matters before the committee today. With respect to all other participants, we ask that in the interest of fairness, that all persons making statements or presentations to this committee disclose any current or previous financial involvement with any firm on whose products or services they may wish to comment. This includes direct financial investments, consulting fees and significant institutional support.

I now would like to turn the meeting over to Dr. Sean Tunis, providing that the mike works, who will give his opening remarks. Then Chairman Dr. Hal Sox will ask the committee members to introduce themselves and to disclose for the record any involvement with the topic to be presented today.

Dr. Tunis: Hal, why don't you go ahead.

Dr. Sox: Thank you. My name is Hal Sox and I will be chairing the panel today. And I'm going to start off by asking each person who's on the panel to introduce themselves, say who you are, what you do, and if you could, if you have any financial

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connection with the subject at hand, this is the time for you to tell us so that everybody understands that. Then I'm going to make a few remarks about the process today, and then we'll hear from Sean.

So, why don't we begin with Dr. Bigger.

Dr. Bigger: I'm Tom Bigger, from Columbia University, and through the years I have had grant funds from several device companies. I don't currently hold any grant funds and I don't have any other relationships that would bear on the meeting today.

Dr. Lee: My name is Kerry Lee, I am a biostatistician from Duke University. I have been involved in cardiovascular clinical trials for a number of years and currently have research support from Medtronic in connection with the NIH funded SCD-HEF trial.

Dr. Carlson: My name is Mark Carlson.

I'm a cardiac electrophysiologist on the faculty at Case Western Reserve University. I too have participated in a number of industry sponsored and NIH sponsored device antiarrhythmic trials. I'm currently a local investigator in Cleveland for the sudden cardiac death heart failure to which Dr. Lee mentioned. I'm on sabbatical at the moment on the

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Senate Judiciary Committee as a Robert Wood Johnson health policy fellow and my activities here today in no way reflect those activities.

Dr. Sox: Did you cover any financial connections?

Dr. Lee: I think so.

Dr. Wilkoff: I'm Bruce Wilkoff, a cardiac electrophysiologist specializing in implantable devices at the Cleveland Clinic Foundation in Cleveland, and I have been involved with most of the trials that we will be talking about today and have had clinical research support through NIH and through each of the tertiary, Medtronic and Guidant through the years and to some degree presently.

Dr. Buxton: I am Alfred Buxton, from Brown University. I'm a clinical electrophysiologist, and I have participated in a number of these trials and received in the past and continue to receive research support from Medtronic, Guidant and St. Jude.

Dr. Curtis: I'm Anne Curtis, a cardiac electrophysiologist with the University of Florida. I have been involved in clinical trials of defibrillators for all three of the major companies and have done some speaking and limited consulting

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work.

Dr. Holohan: Tom Holohan. I'm chief of patient care services for the Department of Veterans Affairs.

Dr. Sox: Any financial interests?

Dr. Holohan: No, no financial interests.

Dr. Flamm: I'm Carole Flamm. I work at the Blue Cross Blue Shield Association Technology Evaluation Center and in that capacity, I did work on the tech assessment of implantable defibrillators.

Dr. Weil: Jonathan Weil. I serve as the industry representative on this panel. As such, I don't vote. I do work as senior regulatory counsel for Philips Medical Systems, which is a leading manufacturer of automatic external defibrillators.

Ms. Greenberger: I'm Phyllis Greenberger, president and CEO of the Society for Women's Health Research. My organization receives funding from some of these major corporations, but I am the consumer rep and as such, I don't vote.

Dr. Krist: My name is Alex Krist. I am a family physician with Virginia Commonwealth University, and I don't have any financial or other interests.

Dr. Matuszewski: My name is Karl

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Matuszewski. I'm a senior director at the University Health System Consortium in the clinical knowledge service. I have no financial conflicts. I might have a few personal ones related to family life but that's a whole different story. Was responsible as a reviewer of an ICD report that we did for consortium members in '97, and that is my primary involvement.

Dr. Redberg: I'm Rita Redberg. I'm a cardiologist at UCSF Medical Center, and I'm director of our cardiovascular women's health services for the UCSF National Center of Excellence in Women's Health, and I have no financial conflicts.

Dr. Conway-Welch: Colleen Conway-Welch. I am the dean of the School of Nursing at Vanderbilt. I have no financial or research interests in any of the interested parties.

Dr. Sox: I'm Hal Sox. I am the editor of Annals of Internal Medicine and as such I don't have any financial connections with anything.

Well, I'm going to make a few introductory remarks to the panel, and I guess the first one is to give you some advice about how to think about this day. For some of you, this is the first time you have participated in a meeting to decide a really important question, which is how good is the evidence

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for intracardiac defibrillators, in a public meeting. And others of you have done this before. I have done it quite a lot since I chaired the Medicare Coverage Advisory Committee executive committee.

And my best advice to you is to forget those people out there, and after a while you probably will, because we're going to get wrapped up in questions of evidence and you're going to forget that they're there. And it's really important that we function cohesively as a panel and that we try to forget that we're in the middle of an open meeting.

Now, our job today is relatively straightforward, compared with the job of CMS. Our job is simply to evaluate the evidence and then to advise CMS on whether that evidence is adequate to draw conclusions about the effectiveness of this technology in Medicare patients. Our job is not to make a coverage recommendation. So all of the issues that, other than the evidence, are really kind of not for us to discuss or really even consider in our, in trying to come to some opinion for CMS. We just focus on the evidence, and in that effect we are fortunate to have a relatively straightforward job. It means that we need to stay focused on the evidence and it's my job as chair to try to keep the

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discussion as focused as possible so that the voting members of the panel can represent the facts in the truest way possible. So, I'm going to use several devices to try to keep us on point and I will go into those in just a second.

Now, the Medicare Coverage Advisory Committee has guidelines for evaluating the evidence and we're going to follow those guidelines. They have served us well in the past and I think they will today, and so I'm going to take a couple minutes to review the high points of those guidelines.

I tried to summarize the interim guidelines for evaluating effectiveness and the first issue is the adequacy of the evidence and it's our job to determine whether the scientific evidence is adequate to draw conclusions about the effectiveness of the interventions in routine clinical use in the population of Medicare beneficiaries, and I've drawn up what I think are the key elements, adequate evidence, effectiveness, routine clinical use in Medicare beneficiaries.

So the first focus then is going to be on,

is the evidence adequate to judge effectiveness, which means in effect, did the conclusions in the studies really represent the facts as they happened,

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in terms of validity. So we're going to be focusing on the question of does the use of implanted cardiac defibrillators change or cause mortality and if so, are the differences in the rate of all cause mortalities with the control group greater than would be expected by chance alone. First of all, is there any kind of effect at all that's beyond the role of chance.

Because we're going to be dealing with randomized trials, a number of sources of bias that might make it difficult to judge that it's the intervention itself rather than confounding variables aren't going to be in play, but we still do have to be concerned about the conduct of the trial and the possibility that the groups that were compared for outcome were different because of differential fallout of patients that caused one group to be really different than the other.

Now the second issue, is the evidence adequate to judge the applicability of the findings to routine use in Medicare beneficiaries? This is the issue of generalizability of the findings beyond the study population to other groups of patients, generalizability or external validity.

Now as you know from reading these

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studies, the authors went to great pains to try to increase the power of the studies by maximizing the proportion of deaths that occurred in the study population who actually died of a cardiac event as opposed to dying of cancer, chronic obstructive pulmonary disease and the like. So they eliminated patients who were likely to die within two or three years of the time of randomization from other causes than cardiac causes, and so we are we going to have to struggle with the question of the degree to which the findings in those studied populations which are effectively clean of chronic disease patients who were on the way to death from another cause, whether it applies also to that group of patients.

We're also going to be concerned, if there is a health effect that's statistically significant, is it an important health effect. CMS is interested in knowing whether the evidence from well designed studies shows an effect size and how it compares with the effectiveness of established services and medical items that they already cover. So one of the things we're going to be doing is trying to characterize the magnitude of the effect size into one of these seven categories that are from the interim guidelines, recognizing that it's possible that we might decide

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the effect size was of a certain magnitude in one population of patients, but different in a different population of patients.

Now, if we find that the evidence is in fact not adequate to draw conclusions about the effectiveness of ICD in all patients or certain groups of patients, we really ought to explain why we thought the evidence was inadequate. That's part of our charge in trying to inform the people at CMS who have to make a coverage recommendation, so it's possible that we will find that the reason was that

it wasn't feasible to apply a definitive study design. That's not likely with the evidence base that we've got consisting of randomized trials, but that does apply to some evidence that CMS considers.

Another possibility is that definitive studies are possible, but haven't been performed perhaps in all appropriate populations. Now if we decide that it's possible to do definitive studies but they just haven't been done in a particular population, then we can give CMS some individual advice about how it might proceed in the absence of definitive evidence.

Now, I'll talk a little bit about how we're going to function today. This of course is

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going to be largely an improvatory exercise but we'll try to impose some order on ourselves so that we can do the best job we can for CMS. In the morning we're mostly going to hear presentations from CMS, from the applicant organizations, from people who have come a long to way to tell us what's on their mind. We can ask questions of the presenters, we can take notes, and the like, but it's really after lunch when we're going to be on our own and at that point we are going to have a structured discussion on the two voting questions. And I guess, Sean, you're going to tell us something about the voting questions in your presentation, aren't you?

Dr. Tunis: Yeah, I will talk a little bit about that.

Dr. Sox: Okay, so I won't go into that now. If we could just put one of those up there, what I would like to do for each one of the voting questions is to establish an agenda, an agenda of items relative to the evidence, and we'll discuss that agenda, perhaps set priorities about which ones we want to spend the most time on. So I would like each panel member to be keeping a list of evidence issues that they would like to have on the agenda for discussion when we get around to the discussion

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period. It's going to be my job to try to move down that agenda of evidence items and try to keep the discussion focused on one item until we finish with that item, and then we'll move on to the next one. So from time to time I may ask you to defer a question until we have had a chance to discuss the agenda item to our full satisfaction.

So, that concludes my introductory remarks. We have a challenging job ahead of us. We for the most part have never worked together before, we're here to discuss a really important issue, and I guess I just ask that we try to support each other, to be as constructive as possible, to remember that ultimately our job is to provide help to CMS to make a very important coverage decision. Thank you.

Dr. Tunis: We're going to move on to Dr. Chin's presentation in just a moment. My name is Sean Tunis. I'm the acting chief medical officer for CMS, and I wanted to also welcome the panel and thank you for all the preparation you have done in advance of this meeting and thank you in advance for your contributions to the meeting today.

As everyone is aware, this is a major issue and a complex issue, and we're going to be struggling with lots of detailed information about a

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number of trials today which will take a lot of your attention. I want to just encourage everyone to make sure over the course of the day that as you hear presentations, that you ask all the difficult questions that you can think of and you make sure that you really understand in as great detail as you need to all of the scientific issues that are going to be placed before you.

What we are counting on you all to do for us is to pore through this data, to pick it apart, to analyze it so that we end up at the end of the day not so much with the, you know, yes or no vote on the adequacy of the evidence, but equally important to that is that we understand where there are questions and have an understanding of what is the level of confidence in the effects that we're looking at, and what is the potential magnitude of the effects we're looking at. Those are equally important to us as what the final vote is on the adequacy of the evidence.

As Dr. Sox was explaining, this exercise today is part of Medicare's determination of whether or not the use of the defibrillators for the MADIT II indications are reasonable and necessary for purposes of Medicare coverage, that's our statutory obligation

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for the Medicare program to determine that. As part of our determination of what's reasonable and necessary is an assessment of the adequacy of the evidence supporting the assertion that there is an improvement in health outcomes associated with the item or service. And so again, I think the exercise today is really focused on having a full understanding of that notion of the adequacy of the evidence.

Before we go on to Dr. Chin's presentation, I just wanted to give the panel a chance to ask any remaining questions they may have about the agenda of the day, the process, what you're supposed to be doing, what we're supposed to be doing, and just give you a chance to ask any questions about that before we dive into the details.

Dr. Sox: Sean, the two voting questions, I wonder if you could comment on those. The second one looks like it's what we came to discuss. The first one as I understand it, deals with an issue that CMS already covers, so perhaps you could explain why that comes to pass and how we should deal with it.

Dr. Tunis: I think that will be clear after Dr. Chin's presentation, and I think his

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presentation will end up with a reiteration of the voting questions. So we'll, it should be pretty clear by the time Dr. Chin is done what the questions are, so if there are no other questions from the panel, we will go to Dr. Chin.

Dr. Chin: Good morning. My name is Joseph Chin, and I am the lead medical officer at CMS on this issue. Today we are going over a lot of data and some details on the articles specifically. I wanted to first provide an outline of what we're going to go over on the presentation.

First I start with the basic background about the current coverage, the coverage request received on this issue, and then I will go and summarize the basic articles that we have on this

particular issue. I won't spend a lot of time, as Sean mentioned, on many of the background articles. I think we will focus most of our time on the MADIT II trial. When we get to the MADIT II, Dr. Goodman will have a presentation, and then I will come back with some final slide and really pose the questions to the panel again.

Medicare first covered ICDs in 1989 but only for very limited indications. The indications in the policy was basically updated in 1991 and 1999.

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The current coverage indications are listed here, basically a documented episode of cardiac arrest due to VF, tachyarrhythmia, and also coverage for familial or inherited conditions that are at high risk. These are published in the Coverage Issues Manual, 35-85.

Last May CMS was asked to expand the coverage of implantable defibrillators to include patients with a prior MI and a left ventricular ejection fraction of less than 30 percent without requiring evidence of ventricular tachyarrhythmias. The basis of this request was the MADIT II trial.

So for this NCD we conducted a basic MEDLINE search from 1989 on using our key words of defibrillator and ICD, focusing primarily on randomized trials and use of the ICD as primary prevention. Some of the trials that we -- we essentially came up with four main trials, MADIT I, MUSTT, CABG Patch, and MADIT II. These trials can be further grouped by use of EP testing, MADIT I and MUSTT required EP testing and CABG Patch and MADIT II did not, so that's I how will present them in terms of their data.

We also included the DAVID trial. It's a little off topic but I think the results were

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relevant to the discussion of ICDs.

So going into the major trials, if there isn't any question about how we got there, the first major primary trial was MADIT I, published in 1996, it was a randomized clinical trial with use of ICDs in patients with a prior MI, ejection fraction less than 30 percent, non-sustained VT, and an inducible ventricular tachyarrhythmia on EP testing. Total sample size was 196, randomly assigned to ICD group and a control group.

And it showed a significant reduction in mortality in the ICD group compared to the control group, 16 percent versus 39 percent, a hazard ratio of .46. These are the survival curves from the article, and if you look at that you will see that you have just about immediate benefit from ICDs and immediate survival benefits.

The second was the MUSTT trial, a randomized trial on antiarrhythmic therapy guided by EP testing in patients with coronary artery disease, ejection fraction less than 40 percent, and non-sustained VT again. Sample size of 704 randomly assigned to antiarrhythmic therapy and conventional therapy. In the antiarrhythmic therapy there was an option for medication or defibrillators, and we had

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people that didn't receive it or were actually receiving it prior to assignment.

The MUSTT results showed a significant reduction in overall mortality in patients who

received ICD therapy compared to patients who did not. Relative risk was .24, confidence intervals listed here, and again, we see this immediate benefit from defibrillators, ICDs. This last curve here is the treatment group with ICDs.

Just to take these two together, really the first question that you will address, these two trials were very consistent with each other, they both had greater than a 50 percent reduction in mortality in the ICD group. They are also pretty complementary since they filled in various gaps that each of the other studies had. For example in MADIT I, the requirement for non-suppressibility on EP testing, MUSTT did not have that requirement, and there was higher beta-blocker use in the ICD group in MADIT I, but the higher beta-blocker use in the control group. And the addition in MUSTT was the creation of a patient registry of the non-inducible patients, which has actually provided a lot of observational data for this subgroup of patients or for those patients that were not inducible.

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Just to summarize these two articles, and we won't talk too much more about them, MADIT I and MUSTT provided adequate evidence on the use of implantable defibrillators in patients with prior MI, reduced ejection fractions, non-sustained VT, and inducible arrhythmias on EP studies. This led to a Class I indication from the ACC, AHA, NASPE guidelines, that were last updated in 2002.

The next two trials are on, or did not require EP testing for enrollment. The first one is the CABG patch trial, so it's a multicenter RCT on ICDs in patients with abnormal signal-averaged ECG, ejection fraction less than 36 percent, and after coronary bypass graft. Total sample size was 900, randomized to the ICD or control group after bypass in the OR.

And the CABG patch trial did not show a survival difference between the ICD group and the control group; the survival curves are overlapping in some places.

There has been I guess a couple comments as to why the CABG patch trial didn't show a benefit. I think one of the ones that has been raised is that CABG or revascularization essentially reduced the risk of sudden death. The trial results reinforced

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benefits of CABG surgery, and Dr. Bigger and colleagues remarked that sustained ventricular tachyarrhythmias may be a better marker for high risk for sudden death then abnormal signal-averaged ECG.

This brings us to the MADIT II trial, the second of the two trials that do not require specifically EP testing. It was an RCT on use of ICDs in patients with a prior MI and ejection fraction less than 30 percent. Total sample size was 1232, randomized at a 3:2 ratio to the ICD and the control group.

And MADIT II reported significant reduction in mortality in the ICD group compared to the conventional therapy group, 14.2 percent versus 19.8 percent, and a hazard ratio of .69, and we have our survival curves from the article. We'll come back to this but as you notice, it looks slightly different than some of the other curves in the other studies and we will come to back to that a little bit

later on.
Some additional findings from MADIT II: 19 percent of the patients who actually got defibrillators received appropriate therapy from their devices, compared to the MADIT I, where 60 percent of defibrillator patients received therapy.

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I guess in other words, in MADIT II over 80 percent of the patients that had defibrillators implanted did not receive any therapy, and I think they were certainly at risk for adverse events, and this is one of the reasons that suggests a need for more appropriate selection of patients.

Also, there was a significantly higher number of hospitalizations for new or worsened heart failure in the ICD group compared to the control group, overall as presented in the article and also in the first 12 months. Why did this occur? I think there has been a lot of debate about that, a lot of theories. I think the DAVID trial we mentioned here provides some insight into what may have happened in MADIT II with these kind of adverse events. In the DAVID trial it was reported that there are significantly higher composite end point of death and hospitalization for heart failure in the ICD patients who received dual chamber pacing compared to backup pacing. I think this issue of adverse events probably needs to be looked at closer by the investigators.

Some additional MADIT II comments. I think one of our major concerns about the trial focuses on the exclusion criteria, specifically the

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FDA indication for the ICD. It appears that the exclusion criteria were not uniformly applied, mainly this issue with MADIT I about the MUSTT type patient with the prior MI, low ejection fracture, non-sustained VT and inducible VT/VF. Holter monitoring was only done on 23 patients and EP testing was not required as an enrollment test, so I guess if these tests were not done on these patients, how would one actually know whether a patient should be excluded or not when they were enrolling these patients. So it's very likely that in the MADIT II population, there are patients that had an FDA indication for a defibrillator with proven benefits in survival. Specifically MADIT I plus type patient, specifically the MADIT I/MUSTT type patients.

Why is this so critical? Well, I think by including a subset of patients known to have a large benefit, really greater than 50 percent reduction in mortality from ICDs, a positive outcome could be shown even if there was little or no effectiveness on the study population. I think this is our main concern with the results and also the trial design in MADIT II.

Well, I guess there are two questions then. How much overlap do you need to influence the

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outcome, and how much overlap actually occurred in the trial. Well, it's unclear on both since the data were not collected, but I think we can get make some fairly good estimates on these numbers. First, MADIT II was stopped early due to a significant finding, and so the actual effect size is fairly small because they stopped the trial, and in this case there's approximately about 10 deaths in the ICD

group, and that's not a lot of deaths we're dealing with. And then even a small overlap of patients potentially influenced the outcomes. And secondly, I think we can estimate the actual number of patients that might be eligible for an ICD based on MADIT I or MUSTT type indications based on the prevalence of non-sustained VT and EP inducibility.

And again, there has been some debate about what this overlap is between the populations. So again, we looked at the literature to try to get a sense of some data that has been presented. Since MADIT II was really a trial on severe heart patients, we looked at the heart failure literature for additional information on the prevalence of non-sustained VT. I found several studies. The first one, the PROMISE trial referred by Chirling and colleagues in 2000 found 61 percent of their 1,080

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patients CHF, an ejection fracture less than 35 percent, had non-sustained VT. And 1998, the CHF STAT study recorded by Sing and colleagues, they found 80 percent of their 666 patients with CHF had non-sustained VT. I also found three review articles that reaffirmed the high prevalence of non-sustained VT in severe heart failure patients. Two of these were by Dr. Bigger, who has probably studied this very extensively, probably more than most people.

On the issue of inducibility, although usability was not required by the MADIT II as an enrolling criteria, 583 patients actually had testing done in the treatment group at the time or prior to ICD implantation. Others, 36 percent were inducible, and actually this 36 percent inducibility rate is almost identical to what was reported in the MUSTT trial. They reported 35 percent inducibility in MUSTT, and all the patients had non-sustained VT.

So our best estimated proportion of MADIT I/MUSTT type patients in MADIT II was in the range of 22 to 29 percent and certainly large enough to influence trial outcomes, given the small actual effect size seen.

We had a number of data issues with MADIT II. Since there was no data on non-sustained VT and

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no actual data on inducibility in the control group, the analysis and actual interpretation of the analysis has been somewhat difficult. We could not just run the question analysis on the data using inducibility as a variable, since when you do this model, essentially it kicks out the entire control group and you're really only looking at your treatment group. And by looking at only the treatment group, it really doesn't tell us about the effect of inducibility on outcomes between the treatment and control groups.

So I guess given these data issues, we asked Dr. Steve Goodman to take a closer look at the data, and his presentation is next.

Dr. Goodman: Hi. I'm Dr. Steve Goodman, I am an associate professor of oncology, epidemiology and biostatistics at the Johns Hopkins School of Medicine and Public Health. CMS asked me to do this analysis for them based on new data that was provided by Guidant to address some of the questions that were brought up here.

Even though my slides are inserted, you will see it has a different format, and CMS had no

role aside from posing the questions in how the analysis was done or how my conclusions were framed.

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And I have no financial interests one way or the other in this matter.

The questions that were posed to me were based on the new data that Guidant had supplied on the EP testing in the ICD population, and this is what we knew from the published data, that there was 14.2 percent mortality in the ICD group and 19.8 percent in the control group. These numbers are based on the two-by-two table, they are not based on the actual survival data, so this relative risk is just very very slightly different than was published, but this is basically numbers we've seen before, about a 30 percent reduction in mortality or a 5 percent absolute mortality reduction, which was fairly significant.

So this was the data, the group data that they had to deal with, and this was the newer data that they were given that Dr. Chin just alluded to. In the inducible group, which constituted 36 percent of those tested, there was 9.5 percent mortality. In the non-inducible group, there was 16.6 percent mortality, and those who were not tested were exactly, or a weighted average of these had a mortality that was almost identical to the overall group, which was 14.5 percent. So this is how

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mortality broke out in the ICD group after testing.

Of course we don't know how it would have broken out in the control group, so there is the problem. What we would like to know is the effect in the inducible group, the effect in the non-inducible group, but what we have is all of the control group being not tested, so all we have is the overall mortality. So the question is, is there any information in this data that allows us to make some guesses about what those might be, and that's the purpose of my presentation. So this is maybe arguably the key number that we're looking at.

So this was the general strategy that we used. The first thing we had to see was in the tested patients, find out if there are other disease or patient characteristics that predict inducibility. That is, is there any information in the data set that might exist in the control patients, those who were not tested, that might tell us the likelihood of their inducibility. If yes, use a statistical model to calculate the probability that each placebo patient was inducible, generate inducibility status for each of those untested control patients with a probability from that model, and then simply use that predicted inducibility status to calculate the ICD

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mortality for the inducibles and non-inducibles. And finally, calculate the uncertainty in those effects, which may be the most important line in the whole strategy.

So, here's the first question. How do inducibles and non-inducibles differ, that is, is there information in other patient characteristics that tells us, gives us a little information as to who's inducible and who's not. For the most part, the answer is no. Almost all of these characteristics, age, gender, percent of diabetes, smoking, hypertension, ventricular arrhythmias and

atrial arrhythmias percent were nonsignificant, but there were three factors that did have some degree of predictive value.

One was, and this is percent negative, the percent where the lowest, NYHA congestive heart failure class, the inducibles had more at a lower class, 32 percent versus 21 percent, this was statistically significant. Similarly, there was a slight difference in average ejection fraction with a fairly significant P value, and moderate difference in heart rate. It was also BUN, even though it's not significant here, there was a slight difference. And we ended up including those four terms in the model.

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We could have included even more since these models don't have to include just significant terms, but these capture virtually all of the information that is going to be there.

So the first thing we want to ask is, that those significant differences actually don't tell you how well it predicts, the next slide tells you how well it predicts, and anyone who is used to looking at curves like this, and I will orient you in a second, will see immediately that it doesn't predict very well.

This is an ROC curve here, sensitivity on this axis, 1- specificity on that axis. When sensitivity equals 1- specificity, that means it's a meaningless test. So a line of complete uninformativity would be a diagonal line across this box right there. So you can see, if that's the line of having no information, this curve which tells us how well this model predicts doesn't give us much more information. The area under the curve is 65 percent and the area under an uninformative curve would be 50 percent, so it's not a very informative curve.

One of the best discriminating points on the curve is right here, and this is a point that

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corresponds to a sensitivity and specificity of 60 percent. So that tells you right away that there is not a lot of information in the other predictors about inducibility, but we used this little bit of information to see what we could see.

So, how did we proceed? Well, there are three sources of uncertainty in the uncertainty analysis. One is just the standard sampling error; this is the error that you get out of any standard analysis. That's the basis for the kind of confidence and key interval values that you see in any typical analysis.

Then there's issues related to the prediction uncertainty, that is, we don't know what the inducibility status of these patients actually are in the control group, so what we know is the probability that they are inducible. So we had to do this multiple times and predict for each individual with that probability whether they were one or zero, and we did lots of analyses, averaging together cases where a person was predicted -- let's say if they were predicted with a probability of 30 percent, 30 percent of the time the person would be included in the analysis as being inducible, 70 percent of the time the person would be included in the analysis as

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non-inducible.

And finally, there is uncertainty in the actual model that you build, and we took care of this by the statistical method of bootstrapping, which is basically doing lots and lots of new samples from the data and rebuilding the model every time and then using that model to predict.

So these are the three components of the uncertainty that will go into the next numbers, and these are the numbers that we got. I'll keep this up for a little bit to orient you since you haven't seen these before.

These numbers you have seen. This is the mortality inducible group, this is the mortality in the non-inducible group. These numbers you've almost seen before, because the mortality in the group overall was 19.8 percent, and so what's happened here is that the model is able to separate these into predicted inducible class only slightly. That is, the model only moves down from 19.8 to 19.1 percent in the inducible class, and moves up the predicted probability from 19.8 to 20.2 in the non-inducible class. This is a function of the model actually not having a lot of information in it.

So we could have predicted -- if we saw

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much more of a separation here, that would actually be a conflict between the predictive power of the model and what we saw. So what do we get out of this? We get an estimated effect, treatment minus control and inducibles of minus .95 percent, that is, roughly a 50 percent reduction in mortality between the control and ICD, which nicely, is almost exactly what we have seen in the trials where EP testing was done.

In the non-inducible group we get an estimate of minus 3.6 percent, which is about 1.7 production, with a confidence interval going from a 9 percent reduction actually up to a 2 percent increase. Here the confidence interval goes from about a 17 percent reduction to a 2 percent reduction, so this in and of itself is statistically significant, this in and of itself is not.

And then finally we have this result for the difference in effects. That's just this number minus this number, that is, how much more effective is ICD predicted to be in the inducible group than the non-inducible group, and we get this number of minus about 6 percent with a very large confidence interval going from a 15 percent change, that is, it would be 15 percent more effective in the inducibles,

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to in fact the other direction, that it's 3 percent more effective in the non-inducibles. So again, not a lot of information.

Now the next few slides are going to give you my guide to how to interpret numbers like this. First, a few caveats. There are a variety of reasonable ways to analyze these data. This was actually the subject for a bunch of lively discussions with my colleagues, and what we all agreed was that it was an extremely interesting problem and could keep statisticians busy for a lot longer than we spent on the analysis, and they'd keep us busy afterwards, after this is done.

So there are several reasonable ways to analyze these data which will produce somewhat different results, I would say not qualitatively

different results but I would not look at the precise numbers here as hard numbers. That is, you could get slight shifts in the variability, you could get slight shifts in the efficacy. None of the different ways we got produced a qualitative change in the way we would look at the numbers, but I just want to point that out, that this filling in missing data is both an art and a science, and there's a lot of ways to go about it.

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I want to point out, survival times were not taken into account. This was not the full data that was analyzed in the MADIT II study. They looked at time to event; we simply looked at whether they died or not. However, I think that assuming that the average survival time in these groups was equal between, in the two randomized groups, we wouldn't expect this to have a big impact, but if we were really going to do this to get all the decimal places as close as we could, we would use the survival times. I think that the assumptions that went in, the variations you will get between methods are probably bigger than the changes you would get if you actually used the survival times.

And finally, this kind of analysis clearly does not substitute for real data on inducibility in a control group, this is not a way of creating a clinical trial with measurements that were not done. It's simply a way of telling us how much, what does the information we have in hand tell us, but it's not the same as actually having that information.

Now here, this is the first -- I labeled this as non-conclusion, because this is a conclusion that I don't want you to make from this data. It is a mistake to interpret these calculations as

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indicating an effect in inducibles and no effect in inducibles. It would be very easy to go back to this and say ah, statistically significant, ah, statistically not significant, something, nothing and that's the end of the story. I would encourage you not to do that, I think it's a more complex picture.

These are the conclusions I can make with moderate confidence, but of course it's for you to decide for yourselves what you think. I think that this does strengthen the finding from MADIT I that inducible patients experience a substantive benefit from ICDs. I think the data provide weak to moderate evidence that the ICD effect is greater in inducible than in non-inducible patients, that's weak to moderate. And I would say that if taken in isolation from the results in inducible patients, the evidence is suggestive but not definitive, that non-inducible patients benefit from ICDs, but probably to a lesser degree than inducible patients.

Maybe the most important twist is this interpretation that I would suggest, which should focus, or which encourages a focus of the discussion on how to use these numbers if you're going to use these numbers at all, not by arguing about statistics, but by arguing about biology. So here's

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my little lecture about that. The adjudged strength of the evidence for an ICD effect in non-inducibles must come from a qualitative biologic judgment about the similarity of the physiologic mechanism and the disease process, of course, producing the treatment

effect in the two types of patients. That is another way to say this is how informative the effect in one group is about the other. So you can ask yourself the question, if you know that it's effective in inducibles, how much does it tell you about its likely effect in non-inducibles if you didn't know anything except the biology. If you judge that they were absolutely identical, that is, both disease processes and the mechanism, the most plausible treatment effect and evidence measure would be from the combined groups, that is, just as published and you would ignore inducibility. If you said that they had completely different mechanisms, that these were basically two different creatures, almost two different diseases in some sense, or that the effect operated in a completely different way, you would say that the treatment effect and evidence has to be estimated for each group separately, and then you could argue about whether this analysis and whether this trial gives you enough data to do that. If the

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judgment is that the mechanisms are similar but not identical, that puts you in a gray zone, in which the evidential strength and treatment effects, both the strength and the magnitude of the effects lies somewhere between the separate and the combined results. Data that's informative about the mechanisms together with results from other trials must be used to make the final determination on that.

So forgive me a little bit of levity, but this reminds me of this cartoon that I saw with these scientists looking at this very complicated board, and one of them says to the other, oh, if only it were so simple. So with that, I'll leave it and Dr. Chin will finish up, but we will both be available for questions.

Dr. Chin: I just had a few other slides to go over, and propose a few questions to the panel then. I think as a summary of the data, an analysis suggests a larger benefit in patients who have EP inducible ventricular tachyarrhythmias, similar to what we were postulating at the beginning. We would actually like them to have run ejection analysis on these data to provide control for these variables, but since we really don't have any actual data from MADIT II on the inducibility in the control group,

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that's not possible, so we had to be through these simulations.

I also wanted to mention that regression analysis of inducibility in the ICD group only doesn't tell us about the effect of inducibility on outcomes between the treatment and control group, since we don't have that data.

Finally, I want to take one more look at the results that we have from the MADIT I and II trials. These are a couple of model survival curves and as you see, they really don't start to separate until after a year. This is not really what we expect from the typical published ICD trials. If we look at MADIT II, we see this immediate benefit from the ICD use occurs, which really leads us to question why did this occur in MADIT II.

I think there's been a number of types of discussion about that, we have one view of that, and I think if we take a look at survival by inducibility, I think this is probably one of the

most interesting slides that we have. This top curve here is the inducible group that received an ICD. This middle one, non-inducible patients in the treatment group. And the last one is the control group. And here you see that the ICD and inducible

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subgroups sort of had this immediate benefit from the ICD, immediate separation of the curves, and this is really exactly what we would expect from a positive trial, it exactly reinforces what Dr. Goodman said and reinforces the results of the MADIT I trial whereas, if you have a really strong group of patients that benefit, or have a really large benefit from the ICDs.

So as a final summary one, in MADIT I and MUSTT, and to some degree the inducible patients in MADIT II that received an ICD, this shows a large survival benefit from ICD therapy for patients with prior MI, reduced ejection fraction, non-sustained VT, and an EP inducible VT/VF. CABG Patch did not show a benefit. Although MADIT II reported a survival benefit, the trial design and data issues may render the results inconclusive. I think that is some of our final points on the issue.

Now going to the questions that we have for the panel, the first voting question, as Dr. Sox mentioned earlier, is related to some of our current coverage policies, but the information is relevant to the question at hand so we have that presented first.

Is the evidence adequate to draw conclusions about the net health outcomes in Medicare

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patients with evidence of a ventricular tachyarrhythmia either induced or spontaneous, with or without documented coronary artery disease, MI and reduced ejection fractions, that receive ICD therapy as their primary prevention of sudden cardiac death. That handful of questions deal with basically trying to get a sense of patients that are really, that really have demonstrated tachyarrhythmias by EP testing. And then the second part of the question is, if yes, what is the size of the health outcomes.

The second question deals more directly with the request that we received for coverage expansion, really looking at expanding coverage to the population that doesn't have any evidence of induced or spontaneous ventricular arrhythmias. The question is, is the evidence adequate to draw conclusions about the net health outcomes in Medicare patients with a prior MI, ejection fraction less than 30 percent and without evidence of an arrhythmia? If yes, what is the size of the net health outcomes from that.

And we have one discussion question, focused mainly on EP testing and inducibility. Two of these trials that we mentioned used EP testing to identify high risk patients, two did not, so the

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discussion question is, what is the utility of EP testing? Thank you.

Dr. Sox: We're going to have an hour for committee discussion and questions for the presenters, but I thought I would give people an opportunity to ask one or two questions, sort of clarification or questions of fact to our first two presenters while it's still a burning question. Does anybody have any questions they would like to address

to them before we go on? Yes, Dr. Bigger?
Dr. Bigger: Just one point I wanted to be sure about. On the third from last slide that Dr. Chin showed, the graph of the survival curve, this one. Is this actual MADIT II data or does this come from the simulations and other statistical work done at CMS?
Dr. Chin: Those curves are from the actual MADIT II data.
Dr. Goodman: The only difference between that and what I did, I tried to separate the control groups. That's a combined control group.
Dr. Bigger: Thank you.
Dr. Sox: Any other questions? Dr. Buxton.
Dr. Buxton: You placed a lot of

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importance, it seems, in the presence or absence of inducible tachycardia. I don't remember seeing anything in the MADIT II protocol specifying the stimulation protocol, and that is critical and if you're going to base any kind of analysis on this, especially in a study that wasn't designed to evaluate the utility of electrophysiologic testing, you'd better be certain that a uniform stimulation protocol was applied, that a standard stimulation protocol was applied across the board. So we need more information on that.
Dr. Sox: Okay. Well, we'd like to make sure that at some point we do present that information, but I think what we should do now is to move on to the requestor's presentation from the Guidant Corporation, and Dr. Joseph Smith and Dr. Arthur Moss are going to share the podium for that presentation.
Dr. Smith: Dr. Sox, members of the committee, thank you very much for the opportunity to be here today. I'm Dr. Joseph Smith, senior vice president and chief medical officer of Guidant Corporation. Guidant Corporation has a long history of consistent commitment to vigorous research in sudden death prevention and has been either sole

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sponsor or co-sponsor of all of the trials mentioned in the summary of evidence that you have before you today.
We appreciate that decisions of the magnitude considered here today, extending CMS coverage for MADIT II patients, often benefit from public discourse. We're delighted to have the opportunity to clarify misconceptions and remove any residual confusion regarding the design, conduct, results and implications of the MADIT II trial. The evidence before you from the MADIT trial is both clear and compelling and is consistent with prior trials demonstrating the life saving efficacy of ICDs in patients at risk. These results have been broadly disseminated and widely accepted.
To frame subsequent discussion, we understand the CMS argument has four major components. One, the exclusion criteria were not uniformly applied and as a result, two, a subgroup of patients with known indications for ICP therapy were enrolled and that this subgroup biased the overall trial results. Three, apparent absence of data on inducibility, particularly in the conventional arm, made it impossible to assess benefit in the

25non-inducible group. And four, in an attempt to
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1assess this mortality benefit indirectly, an
2admittedly limited retrospective subgroup analysis
3was performed, the results of which are inconclusive.
4 Dr. Moss will address each of these
5concerns in his presentation, but at this point I
6think it is vital to point out that from the onset
7that we should not let these speculations distract us
8from the overall results of this large, well done
9randomized control trial.
10 First, it must be noted that the trial
11design of MADIT II constitutes a paradigm shift.
12While previous trials, including MUSTT and MADIT
13focused on EP study results, MADIT II was purposely
14designed without using EP testing as a risk
15stratifier, focusing instead on the reliably
16predictive power of severely diminished ejection
17fraction, in this trial an EF of less than 30
18percent, in identifying a patient population with
19high total mortality and sudden death mortality.
20This design decision was rightly based on concerns
21regarding the poor reproducibility, uncertain
22reliability, and dubious incremental risk
23stratification efficacy of EP study in this already
24high risk population.
25 Subsequent focus on the implications of EP
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1study as a risk stratifier within this group has been
2a source of confusion as it runs counter to the
3fundamental trial design. The analysis provided by
4CMS suggests that MADIT patients were enrolled in
5MADIT II, and this subgroup of MADIT patients biased
6the trial results. To be clear, MADIT II patients,
7defined as those with EF less than 35 percent,
8non-sustained ventricular tachycardia, and inducible
9nonsuppressible ventricular tachycardia EP study were
10specifically excluded. The electrophysiologist
11investigators who enrolled MADIT II patients verified
12that these patients were not MADIT patients in the
13process of performing hundreds of pretrial EP studies
14and excluding those patients meeting MADIT criteria.
15The total of those studies available is 257 negative
16EP studies.
17 The CMS analysis speculates as to the
18potential importance of EP study as a stratifier of
19ICD benefit. In their post hoc analysis of
20non-randomized patients in the ICD arm, they suggest
21that by removal of this collection of inducible
22patients from analysis, the remaining trial results
23are then unclear. This analysis has admitted
24statistical shortcomings. Dr. Moss will address and
25expand on this analysis, providing a Cox proportional
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1hazard model that controls for measurable bias and
2allows for more definitive conclusions.
3 The design of MADIT II does allow for the
4analysis sought in the CMS critique when one focuses
5on only patients who were found to be non-inducible
6on EP study performed prior to randomization. This
7analysis was done by Dr. Moss's group only in
8response to CMS analysis and is based on data made
9available earlier this year. As described
10previously, 257 patients enrolled in the MADIT II
11trial had a prior negative EP study, 113 randomized
12to the conventional arm, 144 to the ICD arm. The raw
13mortality benefits seen in these non-inducible

patients is 54 percent, 19.5 in the conventional arm versus 9 in the ICD arm. This mortality benefit, while numerically greater, is not statistically different from that seen in the entire MADIT II trial. These findings contradict the speculation that a low risk low benefit subgroup might have been identified by a negative EP study.

In this presentation, Dr. Moss will review in greater detail those points I have briefly framed, specifically addressing the issues raised in the CMS critique, namely that the exclusion criteria were uniformly applied, a significant subgroup with known

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indications for ICD therapy were not enrolled and therefore, did not bias overall trial results. There is data on the benefit experienced by non-inducible patients and that benefit appears no different from that seen in the entire population. And a Cox proportional hazard model analysis, when performed on the data used in the CMS analysis, does provide consistent evidence of similar benefit in the inducible and non-inducible arms.

In closing, it is a distraction to focus on what might have been seen had the trials been designed differently, and it is inappropriate to focus on a statistically limited post hoc non-randomized subgroup analysis. It is baseless to imagine that physician investigators, many of whom were instrumental in creating the initial MADIT indications, would fail to identify patients with these indications so that they could then be randomized in this trial. And even in this worst case interpretation of the trial and its investigators, the most appropriate statistical analysis strongly suggests that the trial results would stand unaffected, as the benefit in the non-inducible patients appears no different from that seen in the inducible patients.

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This finding is consistent with the observations which gave rise to the specific design of the MADIT II trial as well as the recently released analysis of the MUSTT investigators in their report on the fate of patients with the same severe level of LV dysfunction. However, this trial should not be evaluated on the basis of these subgroup analyses, but rather on its merits as a well done, large randomized control trial that demonstrated significant mortality benefit in a well defined population.

There is no significant flaw in this study, which has escaped notice by the many investigators, the more than 70 institutional review boards, the Food and Drug Administration, the New England Journal of Medicine, the American Heart Association, the American College of Cardiology, the North American Society for Pacing and Electrophysiology, and the many private insurers who have already made their coverage decisions.

More studies in this area will be done to further define and refine the parameters that identify those who are at risk and then benefit from ICD therapy. This research only makes sense to continue, however, if we ultimately use the derived

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information to benefit the patients.

It's now my distinct pleasure to introduce

Dr. Arthur Moss, professor of medicine, University of Rochester, independent principal investigator of the MADIT II trial.

Dr. Sox: I just want to point out that you have the slides that Dr. Smith presented in your blue packet, as well as Dr. Moss's slides.

Dr. Moss: Dr. Sox and members of the CMS MCAC committee, and consultants, as well as attendees, it's my pleasure to present the MADIT II findings, not only the primary findings, but additional analyses that we have performed both from a scientific standpoint and in response to the questions that were raised by the CMS analysis, and we appreciate the opportunity to bring this to a discussion with our colleagues who have just presented their view of things.

So, MADIT II is a trial that was designed to evaluate the effect of ICD therapy on survival in patients with a prior myocardial infarction and left ventricular dysfunction. Let me just say by disclosure that this trial was supported by a research grant to the University of Rochester by Guidant Corporation. I personally hold no stock or

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stock options in any device company. I'm not a member of any speakers bureau or corporate consulting or advisory group.

What I will present are, my presentation will be in five parts, will give the background rationale, the study design, the results with considerably added information since the primary analysis and publication, then the response to the CMS summary, and then conclusions.

First let me say that there were several versions of the data set but when the trial ended November 20, 2001, we took the first data set in December 7th, the data set which included most of the follow-up data, certainly all of the mortality data never changed. Version II was used in the New England Journal publication. Version III, which was cut July 27th, was a complete follow up after final close-out visits. Version III is the data that I will use in this presentation, and this information was provided to CMS about a month ago.

First, let me emphasize the importance of the reduced ejection fraction and as Dr. Smith said, this does represent a paradigm shift. That is, from many prior studies the ejection fraction is an excellent risk stratifier and with the cut point

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being somewhere below 30 percent and where you have the very steepest incline in mortality. And if you look at ejection fraction in ICD trials, whether it's MADIT I, AVID, MUSTT, CIDS, and now MADIT II, all showed the importance that the lower the injection fraction the greater the ICD efficacy. This is an important point to keep in mind. MADIT II utilized, and is the only trial that used an ejection fraction cut point at 30 percent or below. All of the other trial included patients in this other area.

Now the rationale. When we were designing the trial we felt that patients who had a prior MI and an ejection fraction less than 30 percent would have extensive myocardial scarring and would be at high risk for arrhythmias and sudden death. Also, at the time we were designing the trial, the information from Dr. Sweeney's experience, Michael Sweeney, whose

experience from the Mass General and the Brigham and Women's Hospital reported that EP testing for inducibility, that is, the reproducibility of the test was very poor, with only a 36 or 38 percent reproducibility when the same test was done on the second day. If they had two consecutive days, there was a very poor reproducibility of the test. And this is what concerned us about using inducibility as

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a screening technique, particularly in the low ejection fraction group.

So the study design was the randomization that you know about, the three to two randomization so that we'd have more patients in the ICD group. We used all cause mortality as the end point, and it was a sequential design with preset stopping boundaries and just a slight modification of the group sequential design that is standardly done in almost all trials.

Now the eligibility criteria were eminently simple. Chronic coronary disease with a prior documented myocardial infarction and the low EF. During the first four months or five months of MADIT between July and December of 1997, initial eligibility required frequent or paired ventricular premature beats on a screening 24-hour Holter. All of the first 3 screened patients had these arrhythmias, that is, frequent or paired. None had non-sustained VT. And on the basis of this information, plus the fact that the Holter was inhibiting enrollment, we eliminated the screening Holter on December 31st, '97 after the first 21 patients were enrolled.

Let me just go over quickly the exclusion

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criteria. Was any patient known to have a MADIT I indication which was non-sustained VT, inducibility and non-suppressibility, those were the criteria of MADIT I. New York Heart Class IV enrollment, we waited on enrollment until the patients were at least more than one month post infarct for eligibility. We waited three months after bypass surgery. We eliminated patients who had advanced organ system disease, and that was all spelled out in the protocol. And of course, any of the patients under 21 years of age.

I'm not going to go through all the results. They're in the publication. And the baseline characteristics, I only want to emphasize two things, in addition to the fact that they were, of course, very well balanced. One is that the interval between the index MI at enrollment was about five years, that is the average, the interval was greater than five years in roughly 50 percent of the patients, so we're talking about chronic coronary disease. And the second thing is that this study involved patients with an average ejection fraction of 23 percent. MUSTT had an average ejection fraction of 29 percent. Just to put this in perspective, this is the sickest group of patients

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who have been studied in any randomized trial.

In addition to the Kaplan-Meier curve, and I will make comments later about this separation in the early portion, but let me say that the total mortality was reduced from 19.8 to 14.2, the hazard ratio was .69, in other words a 31 percent reduction

in all cause mortality, and this is the adjusted P value taking into account the sequential design.

Now let me share with you some data that has not been published yet but is being presented at NASPE, we have submitted 11 abstracts and we will try and share with you the information. If we take a look at the cardiac deaths now, we said that the total mortality was 19.8 in the conventional group and 14.2 in the ICD group. If we now just look at cardiac deaths, the mortality was 16.3 in the conventional group and 10.6 percent in the ICD group. If we look at sudden death, it was 10 percent, or actually 61 percent of the cardiac deaths were sudden in the conventional group, and in the ICD group it was reduced to 3.8 percent, that is, 35 percent of the deaths were sudden death in the ICD group. This reduction in total mortality in the overall total mortality from 19.8 to 14.2 is accounted for almost exclusively by the reduction in sudden cardiac death.

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In other words, the device is doing what it's supposed to do.

Now let me show you some additional subgroup analyses. We have now looked at 30 subgroups and we have yet to determine and find any subgroup that differs significantly in hazard ratios. Here we're looking at hypertension, diabetes, atrial fibrillation, left bundle branch block, where the patients were enrolled from, and here you have the mean of the entire population, study population. The mean hazard ratios are by the vertical lines and you see that the all patients, it was .69 and if you look at any of the subgroups, although there is some variation in there, no significant differences between the subgroups and any one of them. So none of 30 analyses that we have done have fallen on the right side of this hazard ratio line. So we have not identified any subgroup that does not benefit from the defibrillator.

Let me just expand a little bit on this. This is a variation of what we presented in the New England Journal article. I just want to highlight the age, that if anything, the older age gets a little bit better effect, lower hazard ratio, but not significantly so. And let me also go to QRS width.

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The QRS width that has been talked about, although the benefit seems to get better with wider width, it is not significantly different, there is no significant difference in the hazard ratios between any of the subgroups.

Let me take this age just a little bit more because Medicare is dominated in part by the over 65 age group. So if we do a subgroup analysis and detail, age greater than or equal to 65, that hazard ratio for this group is .58, so it's lower than the total group. Once again, the sicker patients seem to get the better benefit. In the subgroup analysis we had 75 patients in this age group who had a pacemaker to begin with, before enrollment, before randomization, and they did not do very well. But if you look at the QRS width of .12, .12 to .15, greater than .15, the hazard ratios are in fact identical and there is no significant difference of course in these hazard ratios. So even in the older age group we get the same pattern and if anything, more strikingly so.

Now, let me see if we can respond to the CMS MCAC document. One, the exclusions were not uniformly applied. The MADIT I/MADIT II overlap. The non-inducible ICD patients, what their -- let me

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say, we will show you that in the non-inducible group with adjustment for imbalances, the hazard ratio turns out to be 0.68, similar to the total group. And we'll make some comments on the heart failure question.

Okay, the exclusions. The trial was initiated in July '97 and included the VPBs and the pairs. If non-sustained ventricular tachycardia was found, EP testing was required and patients were excluded if he or she met MADIT I criteria. This was consistently applied throughout the entire trial and there was no patients who to our knowledge of their -- there is no patient with MADIT I criteria that we knew about who got into the trial.

Now the question of overlap. Let me just say that these are the MADIT I criteria, EF less than .35, non-sustained VT, EP inducible, non-suppressible. Here's the MADIT II criteria. Let me show you our best estimate of what exists. If we take the MADIT II group and we go to the best literature we can find, and if we take from Dr. Bigger's article that was published in circulation, taking a look at 24-hour Holters and look at those patients who had an ejection fraction less than 30 percent, 22 percent of these patients

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had non-sustained VT. EP testing in MADIT II was 36 percent that you've heard about. In MUSTT it was 35 percent, that is, who had positive inducibility. VT non-suppressibility in MUSTT was 55 percent. So if you say what was the overlap, 22 percent times 36 percent times 55 percent gives a figure of about 4 percent overlap. We believe that about 4 percent of the patients in MADIT II would have met the formal MADIT I criteria. This is our best estimate based upon this approach.

Now let me go into EP testing, because this was highlighted in Dr. Goodman's talk. And of course EP testing at the time of implant or before implant was the standard of care. Let me comment that the criteria for enrollment that the patients could have had an EP test anywhere up to six months before enrollment, and that information could be used and utilized by the ICD implanting physician as information with regard to inducibility, because many of the doctors did not want to repeat an inducibility at the time of implant. The inducibility was also done sometimes by the catheter technique and sometimes through the defibrillator itself.

Now the major secondary objective of MADIT II clearly spelled out in the published article that

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was published in 1998 or '99 in terms of the protocol was to determine if EP inducibility in ICD patients is associated with a higher appropriate ICD discharge rate for interrogated VT and VF during follow up than non-inducibility. This was in a high level second level objective.

Now let me just say, for those that were done through the catheter, we used a standard criteria for inducibility, and as was pointed out, actually there were 36 percent of the patients were

inducible and 64 percent were non-inducible. Now let me emphasize what is terribly important. The non-inducible patients were in fact sicker with more mortality associated risk factors, a higher percentage with a lower ejection, with a lower New York Heart classification, a higher percentage with elevated BUN, and a lower percentage on the use of beta-blockers than the inducible group. This was highly significant at .03. So the inducible and non-inducible patients were not randomized, so that you have to take into account that the non-inducible group is sicker.

Now let me just take you through this. This is EP inducibility and appropriate ICD therapy either for VT or VF. What we see is that those

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patients who were inducible had a greater appropriate utilization of the ICD therapy for terminating VT. So inducible was associated with an increased utilization of the ICD for treatment of documented VT. However, EP inducibility when we looked at with regard to VF, we see exactly the reverse, that the non-inducible patients had a greater utilization of the device for VF than did the inducible patients. So inducibility depends upon whether, if you have VT, you're going to actually have a greater utilization later on for VT, and if you have non-inducibility, you're going to have a greater utilization for ventricular fibrillation.

Now, some comment was made that there was only 20 percent or 19 percent utilization of appropriate therapy in the ICD arm. Well, that did not take into account the time, and here is the cumulative probability of appropriate therapy for VT/VF in MADIT II patients and in fact, the figure is not 20 percent, it's 40 percent when taking into account the time exposure. And this is an important difference from the raw or crude data that was presented earlier.

Now, if you're talking about the question of non-inducible group, we have to recognize that the

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non-inducible group had more risk factors for mortality than the inducible group. Therefore, the comparison of crude mortality between the non-inducible and inducible is invalid because these two groups differ in risk factors. Now Dr. Goodman presented their approach of trying to estimate how many of the patients in the conventional group might have been inducible, et cetera. We have approached this in a different way. What we have done is we have looked at the non-inducible group and we compared it to the conventional group, taking into account the imbalance in risk factors.

And so this is a traditional Cox model, proportional hazard model, and what we adjusted for, and you can see that the BUN, the New York Heart Association class, the no beta-blockers, each made a very significant contribution to the model. And when we model this taking the adjustment into account, we find that the hazard ratio for non-inducible ICD patients versus the conventional, looking at mortality, had a hazard ratio of .68, which is about as close as you can get to .69 of the total population. So I would like to emphasize this point, a 32 percent reduction in the risk of death per unit time, et cetera, after adjustment for risk factor

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imbalance.
Now let me just show some other supportive data. We have 29 patients where we had absolute documented evidence from interrogation that the cardiac, first cardiac arrest was aborted by the ICD. Okay? And we looked at the distribution, and it turns out that of the 29 patients, 83 percent were in the group that was non-inducible, and this takes into account, this is the interrogation data and of the non-inducible group, they of course had more severe cardiac disease, as I have shown. So the ICD aborts cardiac arrest in more non-inducible than inducible patients.
Now let me talk about a very important thing, pre-enrollment. We found that we had 113 patients in the conventional group and 144 in the ICD group who had non-inducibility before enrollment, and of course then they ended up getting randomized. So this is the best randomized comparison of these patients who had pre-enrollment, negative EP tests, non-inducible, and they subsequently got enrolled into, were randomized to conventional or ICD. And what we see here is the conventional group had a 19.5 percent mortality, the ICD group of this EP negative was 9 percent. And so when we're comparing patients
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who were non-inducible before enrollment, the MADIT II mortality rate in ICD patients is considerably lower than in conventional patients.
So, the summary with regard to EP testing, first, EP testing has poor reproducibility and if one is interested, there was one sub-study by Dr. Helmut Klein who tested reproducibility and found almost the same results as Dr. Sweeney, so that we have non-reproducibility in the MADIT population itself. The non-inducible patients are sicker than the inducible patients. The non-inducible patients receive more ICD shocks for ventricular fibrillation than do the inducible. The ICB aborts VF arrests in more non-inducible than inducible. And when we do the best adjusted analysis, taking into account the imbalances, we get a hazard ratio of 0.68 after adjustment for the risk factors.
Now let me just say a word about heart failure. This has come up. In the total MADIT population we have 244 patients who had heart failure requiring hospitalization. There are many different ways of looking at this, and we have looked at this a dozen different ways. We think the best -- and they all show essentially the same result. We think the best way is to look at the number of patients with
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heart failure events, that is requiring hospitalization, per thousand follow-up months. And the reason for this is because of the increased survival rate in the ICD group compared to the conventional group, there is differential survival, so expressing it as a rate is we think the best way to do it. And in the conventional group it was 8.6, that is number of patients hospitalized for heart failure per thousand months, 10.5 in the ICD group. This difference is not significant, it's a P value of 11.16. And let me say, this analysis is done using a conditional binomial test to account for this differential survival affair, so this is based on rates. But I have to tell you that we've looked at

this many different ways and we get P values ranging from about .15 to about .3, but we never saw any results indicating that there was a significant increase in heart failure in the ICD group.

Let me just comment now in comparing the trials. You've heard these comparisons. This is just looking at it another way. This is MADIT I, AVID, MUSTT, MADIT II, and of course CABG Patch is different. Although the emphasis was well, maybe CABG Patch didn't do inducibility, I personally think that the difference relates to the fact that the

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patients had a defibrillator at the time they were being treated for major coronary disease, angina pectoris, unstable angina with bypass surgery. But all of these others line up very very similar.

And it's my recollection that AVID didn't have required EP testing to come in, so they should have included AVID in the analysis. Once again, patients were not randomized in the MUSTT trial to defibrillator versus non-defibrillator. It was the patients who failed EP suppressibility ended up who got defibrillators.

So let me conclude. In MADIT II population the ICD is associated with a 31 percent reduction in risk of all cause mortality, hazard ratio .69. No significant difference in ICD efficacy between any subgroups that we've looked at, and we've looked at many. ICD patients who were non-inducible at EP had a 32 percent reduction in mortality, that is hazard ratio of .68, after adjustment for imbalances. And MADIT II had minimal inclusion of potential MADIT I patients.

Thank you very much.

Dr. Sox: I think we'll move on now to hear from Marshall Stanton, from Medtronic, and then perhaps time for a couple clarifying questions before

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we take a break.

Dr. Stanton: Thank you very much. I am Dr. Marshall Stanton. I am vice president and medical director for Medtronic's Cardiac Rhythm Management Division. I am a cardiac electrophysiologist and I worked for 10 years at the Mayo Clinic before joining Medtronic.

I have been a member of the MCAC panel for the past three years, serving as industry representative to what was the Medical/Surgical panel under the old MCAC structure. In my experience on that panel, the evidence from a single large, well run, randomized controlled trial like MADIT II has always been acknowledged to be the gold standard. As an industry representative and an experienced clinician, I urge the panel to consider not only gold standard evidence but also practical evidence, the consensus of the practicing clinical community. MCAC and CMS have made great strides to ensure that this perspective, which underlies much of current clinical practice, is carefully considered in the development of coverage policy.

For that reason, I find it especially curious that the CMS Summary of Evidence presents the MADIT II trial in such a negative light. The

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evidence supporting coverage of ICDs for the MADIT II population includes not only the gold standard, according to MCAC's hierarchy of evidence, but also

the consensus of the practicing clinical community. Indeed, the Data Safety and Monitoring Board stopped the MADIT II trial because of the compelling survival benefit of ICDs, and the results were published in the prestigious New England Journal of Medicine. In my experience on MCAC's Medical/Surgical panel, the weight of evidence supporting coverage of MADIT II is unprecedented.

Because I found CMS's summary of evidence regarding MADIT II to be somewhat perplexing, I reviewed the MCAC Executive Committee recommendations for evaluating effectiveness, dated February 23rd, 2001. On page 2 of the recommendation, the Executive Committee notes that, "the most rigorous type of evidence is ordinarily a large, well-designed randomized controlled clinical trial. The ideal randomized clinical trial has appropriate endpoints, enrolls a representative sample of patients, is conducted in clinical practice in the patient population of interest, and evaluates interventions as typically used in routine clinical practice."

The MADIT II study clearly fulfills all of

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these criteria. The study was large, well designed, randomized, controlled and adequately powered. The results were strong -- a 31 percent relative mortality benefit. Half the enrollees were Medicare age.

MCAC has historically viewed one large, well-designed randomized controlled trial as adequate evidence for coverage. In fact, small non-randomized trials have been viewed as adequate evidence. The MCAC guidance document goes on to say, "If the evidence is adequate to draw conclusions, the next question is the size and direction of the effect compared with interventions that are widely used." The magnitudes of effect size that merit coverage are described as one, the improvement in health outcomes is so large that the intervention becomes a standard of care, or two, the new intervention improves health outcomes by a significant albeit small margin as compared with established services.

As previously stated, the MADIT II effect is 31 percent relative benefit for the overall trial and 9 percent absolute mortality benefit at three years of follow-up on the Kaplan-Meier curves. I think it's important to look at those curves, as CMS and Dr. Moss have pointed out, so perhaps we will

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have more discussion on it. That magnitude of life-saving effect is far in excess of other medical therapies that are widely considered standard of care, including beta-blockers for post-MI prophylaxes and ACE inhibitors for heart failure. In that context the magnitude of effect size is a one by MCAC's definition. Indeed, this could be considered breakthrough technology for this patient population.

Finally, the MCAC guidance document tells us, "The process is intended to serve the public by identifying medical goods and services that improve the health of Medicare beneficiaries." This study shows a definite improvement in health and clearly identifies a patient group able to benefit from this therapy. Patients are easily identified and risk stratified by a previous myocardial infarction and an ejection fraction less than or equal to 30 percent. No other methods of risk stratification, including

signal average ECG, T-wave Alternans, QRS duration or EP study have been shown in randomized trial to further define who would benefit to a greater or lesser degree from ICDs. This should not be confused with the fact that EP testing has utility in different patients and for other reasons in this patient group.

CMS has proposed that we ignore the results of a trial that was well designed and well run, by their own MCAC guidance criteria, and instead accept guesses as stated by Dr. Goodman, and a post hoc analysis based on the inappropriate removal of 36 percent of patients from one arm of the study, and 1.6 percent of patients from the other. We are asked to accept the argument that since the percent inducible patients is similar in MUSTT and MADIT II trials, and only inducible patients were allowed in the prior studies, that somehow that means that only the inducible patients in MADIT II benefited from the therapy. In conjunction with removal of patients, CMS performs the questionable practice of subsetting the MADIT II patient population below adequate statistical power and then highlighting the resultant nonsignificant difference as a meaningful finding. Their conclusion is unsupported in addition to their methodology being unscientific.

If the situation were reversed and a requestor came to CMS saying our study didn't show anything, but if you're just willing to make the following assumptions and selectively remove some data, we might just have something here, then there would not be an MCAC panel meeting today. This

approach is clearly not accepted by the FDA, nor by peer reviewed medical journals.

Further, the CMS argument is based on the supposition that EP testing can risk stratify people into those who are at high risk of death and those who are not. EP testing is no longer accepted as an appropriate risk stratifier in post-MI patients by the medical community. This is based upon the scientific literature, including last year's publication of further data from the MUSTT study from Dr. Buxton. Those data show that in patients with an ejection fraction of less than 30 percent, those people who are inducible at EP study and not treated have a five-year mortality of 57 percent, and those who are non-inducible have a five-year mortality of 54 percent.

The MADIT II data are consistent with and add to the body of literature supporting the use of ICDs as primary prevention in this patient population. The CABG Patch trial is an excellently run study and it provided important information which is adopted into clinical practice. It identified a group that does not benefit from prophylactic ICD use, that is, patients with low ejection fraction, positive signal average ECG, and requiring

revascularization, a group excluded from MADIT II.

As I mentioned, CMS and MCAC have historically considered consensus of the practicing clinical community as an important element of the evidence base when considering questions related to coverage. The three relevant medical specialty societies, NASPE, the American College of Cardiology,

and the American Heart Association have weighed in on the MADIT II results with a solid IIa recommendation in their recently updated guidelines. The European Society of Cardiology gave a IIa recommendation in their guidelines as well.

CMS has often used Blue Cross Blue Shield TEC assessments as the basis for determining coverage policies. Blue Cross Blue Shield TEC recently found that the MADIT II indication met all five of its technology assessment criteria. Blue Cross Blue Shield TEC says the MADIT II evidence is sufficient to provide coverage to 85 million covered lives. Aetna and Kaiser already cover MADIT II patients without restriction. In total, more than 115 million non-Medicare patients have or are recommended for MADIT II coverage.

Numerous organizations with rigorous evidence-based medicine processes have reviewed the

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same clinical data that are before you and have concluded that coverage of the MADIT II indication is appropriate. Medicare beneficiaries should have the same access to life-saving technology that's widely available to non-Medicare patients. To deny Medicare beneficiaries access to this therapy creates a second class healthcare system in the United States.

Finally, I would like to thank CMS for the opportunity to present, and to ask the panel to support the MADIT II evidence and to allow unrestricted coverage for beneficiaries meeting the MADIT II indication. Sudden cardiac death occurs in about 450,000 people in the United States each year. It is the single largest cause of death, greater than deaths from AIDS, breast cancer, lung cancer and stroke combined. Patients with this indication are dying every day and the study has already been out for almost a year. Coverage will save lives. I ask that rapid action be taken by CMS to institute coverage and that my presentation be incorporated into the record. Thank you.

Dr. Sox: Thank you, Dr. Stanton. We'll now treat ourselves to a ten-minute break, and resume at five after ten.

(Recess.)

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Dr. Sox: We've got the next 40 minutes or so to ask questions of the presenters so far. And perhaps what I should do before we resume is just remind you that the group that's up here behind the microphones will function as a panel of one, one panel, up until the time that we basically take a vote, and at that time the five individuals to the right of Dr. Curtis will not vote and it will be just up to the people down here to vote on the question, a question of one.

Sean Tunis asked for a moment to make a few clarifying remarks before we jump into the discussion. Sean.

Dr. Tunis: I just wanted to make sure that the committee understood, as well as the guests here understood that the document on the, the analysis by the CMS staff produced and distributed to you and the presentation by the CMS staff represents the interim work they have done, it is not a near policy nor a policy document, and it should be taken as nothing more than an attempt to provide you all with some of the issues, some of the underlying

issues that need to be discussed as you come to your voting question.

The whole sort of premise of the coverage promulgation process is to have the opportunity for public discussion and back and forth on some of the more complicated issues. I think the, just to respond directly to the implication that there is some lack of legitimacy about having this meeting at all, I remind the committee that these recommendations by the ACC, AHA and NASPE on this is a two-way recommendation and that there is conflicting evidence, or conflicting in the sense that it is not a Class I recommendation that there is consistent and multiple studies and consistent expert opinion of the value of the intervention. A two-way recommendation from the ACC reflects the exact same uncertainties about the analysis of the evidence that we are here to consider, and that's the purpose of this meeting.

So again, two points to make, which is that the CMS document was publicly distributed for purposes of living up to CMS's commitment to have these issues discussed in public, and that the purpose of this meeting is to fully explore the acknowledged uncertainties in the evidence that represent the opinions of the American College of Cardiology and other organizations, as well as CMS's issues.

Dr. Sox: Before we begin discussion, I would like to make an observation that might help us to focus a little bit. The CMS analysis was sort of predicated on the notion that there may be important large subgroups within the MADIT II study which differ in their response to the therapy and which can be identified by EP testing. The two, the requestor presentations seemed to me to focus on the idea that EP is not a particularly good way to identify subgroups of post-MI low ejection fraction patients in a way that predicts their response to the therapy. So, it's really crucial to get to the bottom of this question of whether EP really helps at all because it is in a way at the heart of the presentation that Dr. Chin and Dr. Goodman made, and the contrary assertion was at the heart of the presentation by the requestors. So I'm beginning to think in my own mind that that's a question that we need to focus on in this discussion.

So with that said, and not meaning to limit the discussion at all but simply to raise that point, does anybody have any questions they would like to address to any of the presenters? Yes, Dr. Curtis?

Dr. Curtis: I wanted to ask Dr. Moss for a point of clarification about the MADIT II. Were patients systematically screened for MADIT I type indications prior to enrollment or not?

Dr. Moss: The answer to that is no, we did not do Holter recordings on all the patients to get into the trial. That would have -- when we tried to do this initially, it inhibited enrollment. And then further articles surfaced, actually referred to in the CMS document, the articles by Dr. Steven Sing and others that we have the articles here, where the conclusion is that non-sustained VT has no

predictable ability to discriminate endpoints.
Let me just take one minute to answer that. This is from Dr. Sing's conclusion. Non-sustained ventricular tachycardia, this is now in patients with heart failure, was not an independent predictor of all cause mortality or sudden death, and then -- that was in Journal of American College of Cardiology in 1998 -- and then in Circulation in 2000, Tirlenk et al from the PROMISE study, that is the ambulatory ventricular arrhythmias in patients with heart failure, this is the title, do not specifically predict an increased risk of sudden death. So the answer is as evidenced, we initially had the 24-hour Holter screening but after the first

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five months, that was eliminated and that was discussed with the FDA.

Dr. Curtis: And as a follow-up to that, it did appear that there were patients who had had EP studies before enrollment and if they were negative they were eligible for MADIT II. So does that mean then that if a patient happened to have been identified with non-sustained VT, if you happened to pick it up on telemetry, then an EP study was required and they only got in if they were negative?

Dr. Moss: That is exactly correct. Anybody who had non-sustained ventricular tachycardia identified in any way would undergo EP testing and had, if they were inducible and not suppressible, they were excluded from the trial and they had a defibrillator implanted as part of the approved protocol and they were not part of the trial.

Dr. Curtis: Thank you.

Dr. Sox: If I could ask a follow-up question, Dr. Moss. You nonetheless accumulated a fair number of patients that were inducible and presumably they did not have non-sustained VT. How did you come to find out that they were inducible? Was that because you performed EP studies on them for some other reason?

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Dr. Moss: Well, I think the best answer I can give is that frequently in patients who had low ejection fraction, physicians were doing inducibility studies and if they found that they were inducible and not suppressible, even though they didn't exactly meet the MADIT I criteria, they frequently had ICDs implanted. This is unrelated to the study. I mean, they just screened them out, so that there were groups around the country who were trying to screen patients both with, some with Holters, but frequently just on the basis of vague symptoms of palpitations or near syncope or dizziness, who had low ejection fractions and if in fact they were found to be inducible, these patients very frequently received an ICD and never got to us. I'm not sure that's an answer to your question.

Dr. Sox: Well, yet the --

Dr. Moss: Oh, the inducible patients who are in the study?

Dr. Sox: That were in the study, the enrolled patients, how did you find out that they were inducible if you excluded all the patients who --

Dr. Moss: They were inducible after enrollment, after randomization into the ICD arm.

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And there were a small group of patients who may have been inducible prior to entry into the study who got randomized into one group or the other. It was just a matter of -- Dr. Hall, do you want to respond to this?

Dr. Sox: Maybe I could ask the question another way. In your study protocol, did your study protocol say anything about the performance of EP studies in patients who enrolled in the study, did you have a standard approach?

Dr. Moss: Only in that it was in the ICD group, it was recommended that they have an EP test at the time of the ICD implant. That was the only recommendation. The decision as to whether they did that or not was left up to the implanting physician.

Dr. Sox: And was there any decision made if they were found to be inducible or not inducible after those studies, was there any provision made about taking them out of the study, or did everybody stay in?

Dr. Moss: Everyone stayed in and they were followed entirely with intention to treat.

Dr. Sox: Thank you. Dr. Redberg.

Dr. Redberg: I'm looking now on the slide on the data comparing the inducible versus

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non-inducible from the MADIT II data, to the ICD mortality where it differed from 9.5 to 16.6 percent, and I understand that those obviously weren't randomized. But I do also believe that, you know, and certainly I agree with your statement before that the main expectation would be reducing arrhythmic deaths by use of the defibrillator because that's obviously what it's going to do, and that if you do believe inducibility is a predictor for arrhythmic deaths, and it's certainly what I have been taught through my cardiology training, then it does sort of seem from the data and also from what you would expect that you would have a greater reduction in mortality in inducible than in non-inducible patients.

You did point out that the non-inducible group had more comorbidity because it wasn't a randomized group, and I'm sure that's true, although I also expect that in general, if you compared a trial population to the Medicare population, they're going to have a lot more comorbidity because trial patients are always healthier than the patients we actually see in our offices. And so I'm wondering, so it's my, you know, take from this slide and the data we have, and I understand we don't have the date

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on the control group, but it certainly seems to me that inducibility does separate the mortalities there because there's a big difference in mortalities such that the non-induced mortality really is a lot closer to the control than the inducible group. And I'm just wondering if there is any other information that you would have that would tell me that that's not a reasonable assumption.

Dr. Moss: Well, the assumption is partly complicated by the fact that the non-inducible group is sicker, so you have to take that into consideration. And when you take that into consideration, the inducible and non-inducible groups behave in a very similar way. So if you just look at crude raw mortality and not take time into

consideration, then you get a very biased and what we think is a somewhat, not somewhat, an inappropriate conclusion, because those patients were not randomized.

With your earlier comment that inducibility has been the standard for identifying patients with sudden death the question is, how do you come to grips with a test that has very poor reproducibility. And any statistician who I speak with, that when they see a reproducibility of 38

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percent, they tell me there is no way you separate the two groups because if you can get, have such a poor reproduction when doing the same test the next day, then how can you realistically use that test.

Now I showed the data from Dr. Michael Sweeney's presentation from 1997. That was what we drew upon when we designed the trial. Dr. Helmut Klein, and I will be glad to show the slides, did a similar reproducibility, but he used a longer time interval between the testing and he came to almost the same conclusions, that they could not get the patients who were inducible at one time when studied the next time, had a very low likelihood of getting the same result. And when you have that type of a test, I don't see how you can use it as a discriminator for patients. So if we have 36 percent of the patients who were inducible at one point in time and as Dr. Buxton pointed out, these were done sometimes through the defibrillator, sometimes with a catheter, sometimes within the six-month period before, so the trial wasn't designed to ask and answer that question. But in a test that's not reproducible, I don't know how one can use that as a screening test.

Dr. Redberg: That's interesting to me.

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It appears to me that Sweeney is an abstract, and I don't know if that has been published in full manuscript form.

Dr. Moss: I don't think so.

Dr. Redberg: And I think you would agree that EP study has certainly always been used, or certainly we have always been taught in practice as a very reliable way to predict arrhythmias and you know, we have structured, all the other trials had EP testing I think for that reason, because EP studies have been considered to be important. I certainly don't think we do have good reproducibility data, but I also do think that there's clearly a difference between that inducibility group and the non-inducibility group, and to say that even if it's not that and due to comorbidity, as I said, I do have concerns that the actual Medicare population would certainly have a lot more comorbidities than the MADIT II patients.

Dr. Moss: I'm not sure exactly how to respond to that other than to say that even within MADIT II we could not find the reproducibility in these patients who were -- this is Dr. Helmut Klein's work and if you want I will be glad to show you his data that is being -- well, we submitted it for

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abstract presentation at NASPE, and it's in preparation for manuscript, so I'm not sure -- oh, the only other comment is virtually all of the inducibility testing when you go back historically

have been done on patients with relatively good ventricular function.

That is, when you go back to Mark Josephson and Leonard Horowitz studies of inducibility, it was the fact that inducibility into VT predicts subsequent VT in good risk, relatively good risk patients. Nobody has really concentrated on this extremely severe group of patients with an average ejection fraction of 23 percent. That seems to overwhelm the issue of inducibility.

Dr. Redberg: I'm just trying to, if you could explain the 19 percent, the result that says 19 percent of patients got implantable defibrillators actually received appropriate therapy. I don't understand how that data is the same as this date showing probability of first therapy, which looks like it goes up to 40 percent at four years.

Dr. Moss: I will be glad to give you my comment on that and I would like Dr. Hall to comment also. The difference is they just took the numbers not taking time into account, that is, the time of

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occurrence as you go out in time, the numbers get smaller. That is the denominator, so that the Kaplan-Meier survival curve or occurrence curve is a much more accurate reflection of what is going on. It's very similar in a way to the Kaplan-Meier mortality curves. You have to take time into consideration. But I'm going to ask Dr. Hall to make a comment.

Dr. Hall: My name is Jack Hall. I am a statistician for the University of Rochester, a statistician for MADIT I and MADIT II studies, which were of course sponsored by Guidant. The two statements by the CMS report and Dr. Moss's are not in contradiction. The 19 percent of the patients, if I assume that's a correct figure, did have utilization but of course some patients were only in the trial for a month, others 6 months, others 12 months, others three or four years. And indeed, the Kaplan-Meier says at the end of four years, by the time that four years have elapsed, 40 percent will have made good use of the defibrillator. The 19 percent figure you have to keep in mind, on average, the patients were only followed for 20 months.

Dr. Redberg: So you changed the denominator.

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Dr. Hall: If you look at Dr. Moss's Kaplan-Meier curve, and looking at 20 months, you will probably see something like 19 percent.

Dr. Sox: Dr. Matuszewski, you had a question?

Dr. Matuszewski: Yes, for Dr. Moss. Dr. Moss, can you give me a sense of how many patients were screened before the 1200 plus were enrolled in MADIT II?

Dr. Moss: I don't think we have an accurate denominator on that. As we point out in the article in the New England Journal, we attempted to keep logs of the patients who were screened. That just did not function as such in the way the patients were referred, because they came from so many different sources. They came from clinical cardiologists who referred their patient to the electrophysiologist. They came from radionuclide and echocardiographic laboratories. So the number that

were screened was probably very large, but we do not have an accurate number on that.

Dr. Matuszewski: Do you have any sense how many were excluded because they met MADIT I criteria?

Dr. Moss: I don't think I have an

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accurate number but let me just check with and see if any of my colleagues have that number. It's a number that's less than double digits, somewhere in the 7 or 8 percent, but we don't have that number.

Dr. Matuszewski: And then two more quick ones. 3.8 patients per center enrollment, is that accurate, for the 72 centers?

Dr. Moss: You know, I don't -- I mean, it's whether you're taking a mean or a median or what.

Dr. Matuszewski: That was per year enrollment?

Dr. Moss: But as a mean figure, overall the total group we had 76 centers and an enrollment over four years to get roughly 1200 patients. We had some centers that enrolled 20 or 30 patients, some that enrolled 50 patients, and some that enrolled a few patients. And the analyses that were provided adjusted for and took into account the center effects. Dr. Hall, would you like to comment on that?

Dr. Hall: Yes. On average, 16 patients per center over four years.

Dr. Matuszewski: Finally, was there any clustering at centers, or individuals who performed

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the EP studies, either post-implementation or prior to, so was it an effect of the 500 studies that were done were the result of a handful of clinicians?

Dr. Moss: No, that wouldn't be the case. This was, each center had roughly three or four co-investigators, electrophysiologists at the center who were involved in the implantation. There was no heavy concentration in any few centers that dominated the results or dominated the EP inducibility. It was, I would say reasonably distributed across the wide margin of centers.

Dr. Sox: Dr. Flamm.

Dr. Flamm: This question is to Dr. Moss. I would like to clarify and understand the difference between the results that you presented on pre-enrollment EP results and the non-inducible, the patients who were non-inducible on EP, and then subsequently randomized into the conventional and the ICD arms. And there were a total of 257 patients, of which 113 were in the conventional arm. I would like to understand the difference between those data and the data that Dr. Goodman used where all the EP results were in the ICD arm and I think virtually none of the EP results were in the conventional arm. So, are we talking about the pretrial EP results were

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not made available in the analysis that Dr. Goodman did? And I would like to clarify that, because we basically have --

Dr. Moss: I don't know precisely what Dr. Goodman did. I can tell you what we did. We thought it was important to compare apples with apples, and so we took the patients who had a preceding non-inducibility, preceding formal randomization. So

we had accepted up to six months before for patients, we could go back for patients who were randomized, what their EP studies were prior to six months. That was in the original design of the protocol. So that group who had EP testing before and subsequently then were randomized, we thought that's the best way to compare apples with apples, because randomization tends to make sure that you have the same risk distribution and risk factors. And so that's what we thought was the most appropriate way.

We thought there were two appropriate ways. One was to look at the group of patients who had EP testing before and subsequently, and then got randomized. And the second was taking all the patients who were non-inducible, finding out that they were sicker, adjusting for risk factor difference between that group and the conventional

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group, so that we took into the risk factor mortality risk factors. And that's when we ended up with a Cox hazard ratio of .68, a 32 percent reduction in mortality in the non-inducible group with ICD therapy when adjusted for mortality risk factors, because the non-inducible group was clearly a sicker group.

Dr. Flamm: Okay, I understand. Is there anybody else from Guidant, whoever provided the data used by Dr. Goodman, to know whether those pretrial non-inducible patients were included in his data set?

Dr. Moss: Well, we provided CMS with the entire complete data set, they had all the information. They worked for the most part off of Version II, which we did for a long time. Version III was only a slight change, and they had available to them Version III. I think you should really ask them. I don't know what they did. I know they had the same data that we did and the same data was available.

Dr. Sox: I think Dr. Curtis was next. Anybody who wants to be recognized, just raise your hand so I can get you.

Dr. Curtis: It sounds like the majority of the EP tests that were done as part of the MADIT trial were at the time of ICD implantation through

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the ICD; is that correct?

Dr. Moss: No. The majority were done through catheter. A small percentage, I can give you the specific figures, but I think it was only 8 percent that were done through the ICD. I will find those numbers and give them to you, but go ahead.

Dr. Curtis: And was there a standardized protocol recommended?

Dr. Moss: Yes. The standard protocol was the protocol that Dr. Jay Mason had used in their study that had been previously published and had been utilized, and it was the same protocol that we utilized and recommended and made it one. So it was a through the catheter protocol at two sites, two cycle lengths, so it was exactly the established protocol. We can go on with the questions, but I know that we have that breakdown of the numbers.

Dr. Curtis: You have standard definitions for VT/VF and what was considered?

Dr. Moss: Yes. I showed that on the slide, that is, with double stimuli we would accept VF, and with triple stimuli VT or sustained polymorphic tachycardia.

Here, I have it right here. Through the ICD my recollection was correct, 8.2 percent.

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Dr. Curtis: Okay, thank you.

Dr. Sox: I think Dr. Lee was next.

Dr. Lee: I would like to follow up on the question we were discussing with the previous panelist, and that has to do with the data that was on Dr. Smith's slide with these EP negative patients. The pretrial EP negative patients shows there are 113 of those in the conventionally treated patients, but yet in the document that we received, the CMS evidence summary, it indicates that there were only 112 patients in the control group that had EP testing. Could we get a clarification of that apparent discrepancy? And that's simply because this issue of inducibility and EP testing seems to be a fairly critical issue in this discussion.

Dr. Moss: Dr. Hall, do you want to first respond to that as you understand it?

Dr. Hall: My understanding is that the 12 were identified as inducible during the trial and not -- the 113 you refer to was a different set of data, different form, whatever, it was all about pretrial activity, and so that 113 is pretrial. The 12 is post-trial.

Dr. Lee: I think it must be those 12 patients that were the basis of the data that

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Dr. Goodman was looking at. Could I just ask Dr. Goodman a question.

One of your slides indicated that based on your analyses that the data provided as you characterized it, weak to moderate evidence that the ICD effect is greater in inducible than non-inducible patients.

Dr. Goodman: Right.

Dr. Lee: As I go back to the New England Journal article that Dr. Moss and colleagues published, if you look at some of the subgroup analyses that were reported in that manuscript, in particular for example, the breakdown according to different age categories or the breakdown according to the width of the QRS interval, you see differences in terms of the hazard ratios, they're numerically different at least according to the paper. There were apparently formal tests performed for statistical interactions and none were found to be significant. Yet, I can see just from looking at that plot of the hazard ratios that the absolute difference in mortality rates between for example the patients who were 60 to 69 years of age is going to be considerably less than the absolute difference in mortality in the patients who are less than 60 years

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of age.

So, I have two questions. One is, based on your predictions of inducibility and as you look at inducible patients compared to non-inducible patients and the differences between the treatment effect in those two groups, did you attempt to evaluate whether there was an interaction, a statistical interaction present, or did you feel that that was sort of carrying the predicted inducibility analysis too far?

Dr. Goodman: Well, the last term on my slide, which is the difference of the two effects, is

the interaction term, and that was what the basis for that comment was.

Dr. Lee: You didn't tell us whether that was statistically --

Dr. Goodman: Well, I have the confidence interval there. It was not, which is why it was characterized as weak to moderate evidence. The absolute difference in effects would be minus 5 percent with a confidence interval, you actually have it there, of relatively minus 12, I think, to plus 2, or somewhat broader than that, and I think the P value was about .2. So it included a zero difference, which is why I couched the, or made the

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warning against interpreting the subgroup effects in isolation from each other.

Dr. Lee: Okay. I understand your reason for stating then that it was perhaps a weak to moderate effect. As we look at some of the other subgroups that were examined, Dr. Moss and Dr. Hall, in your New England Journal of Medicine paper, would you also conclude that your data provide weak to moderate evidence that the ICD effect is greater in patients who are 60 to 69 years of age, compared to these that are less than 60 years of age? In other words, I'm just trying to put all of these various subgroup analyses into some kind of perspective and I'm just interested in what you would conclude from your New England Journal subgroup analyses compared to this subgroup analysis that we've heard today relative to inducibility.

Dr. Moss: Well, let me say that first, we found no statistically significant interactions within any of the subgroups whatsoever, and we looked at that. Now, granted that the trial was predicated on looking at total mortality as the primary endpoint, but in many trials that are performed, one frequently finds a subgroup that doesn't behave properly, in which the mean hazard ratio falls on the

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other side of the hazard, on the one value above one, and that you can get a bidirectional interaction. We found none of that in this study.

Dr. Hall did most of the interaction analyses and maybe would like to make a comment.

Dr. Hall: It's hard to have any standard of what is weak or moderate evidence. My views would differ from Dr. Moss's which would differ from Dr. Goodman's, I'm sure, so I'm not sure what can be said about that. And certainly the once you refer to, I think most of us might well disregard because it seems so peculiar that the under age 60 does well, the 60 to 69 doesn't look quite as good, and then the over 70 looks good again. It doesn't make sense that the 60 to 69 are somehow different. And in later analyses we've cut at 65, especially for this group, and there 65 and above looks like it's a lot better than the under 65s. I would call that, maybe that's weak evidence, but it's certainly not a statistically significant difference.

Dr. Lee: The reason for the question is to try to give the committee a flavor for the credence that we put into this analysis of inducible versus non-inducible patients, because it's another subgroup analysis basically, although it was arrived

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at through a much more indirect route.

Dr. Goodman: I also want to point out that even if you have an interaction term there, as you know, it doesn't necessarily mean that the effect in the non-inducible was zero. They could be different and still both be non-zero, so the presence or absence of the interaction term isn't necessarily the end of the story.

Dr. Sox: They could be not only different and non-zero, but they could be clinically important.

Dr. Goodman: Right. They could both be beneficial to a different degree.

Dr. Sox: Okay. Dr. Krist.

Dr. Krist: I have two unrelated questions and the first is going back to the data on the pretrial EP negative population, and this is for Dr. Moss. I was interested if you have any information about how similar that group was to the general MADIT II population or to the folks who were EP negative when they were tested in the context of MADIT II, as far as age or CHF status, or if there was a difference in this population compared to general MADIT II population.

Dr. Moss: We have not specifically looked at that. However, since the patients were

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randomized, we would assume that they were quite well balanced. And so your question is with regard to the pre-enrollment EP non-inducible group that subsequently got randomized to either ICD or non-ICD, how they compare with any of the other groups and whether the two groups ended up, that is within the ICD and non-ICD arms, whether they had equivalent clinical makeup or not. We just don't have that information. There would be no reason to believe that they would be different, since they were randomized.

Dr. Sox: I have actually stuck myself in with a question at this point. You calculated a hazard ratio of I think .68 for ICD in non-inducible patients, Dr. Moss, and I think I can understand how you calculated the numerator for that, that's the ICD group. But I'm having trouble figuring out how you figured out the death rate in the non-ICD group of non-inducibles, since presumably you were facing the same problem that Dr. Goodman did in trying to come up with a reliable calculation for that.

Dr. Moss: I think we can give a very specific answer to that. Dr. Hall?

Dr. Hall: Yes. That .68 is a comparison of the non-inducibles in the ICD group with all

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patients in the conventional group, but takes into account and adjusts the computations for the differences in risk.

Dr. Lee: I thought it was impossible to take into account the inducibility status, that's one thing you could not include in your model.

Dr. Sox: Right.

Dr. Hall: Right, that's right. We do not take into account inducibility status in the conventional group because it's unknown.

Dr. Sox: So it's not strictly comparable comparison, it sounds like. That's Kerry's point.

Dr. Hall: In one sense not strictly comparable, but in another it's comparable in the sense that it has been adjusted, it's standard statistical practice in any observational study to

adjust for differences between the two groups being compared.

Dr. Sox: Right. Okay. The next one is Dr. Buxton.

Dr. Buxton: I think I can amplify on some of the data that Dr. Moss was speaking to regarding reproducibility of tachycardia induction. There are six published, not abstracts, but published studies in patients with myocardial infarction between one

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and three months prior to the EP study that uniformly showed 80 percent reproducibility in those results. You could take as an adaptation data that Dr. Moss quoted from the MUSTT trial, regarding inducibility, if you looked at the patients who had inducible tachycardia in that trial, were randomized to EP guided therapy and went through electrophysiologic testing on drugs. 55 percent were inducible on drugs, so there is at least 55 percent inducibility even in the presence of a drug, and undoubtedly the drug suppressed the inducible arrhythmia in some of these.

The answer is that it's still not very high and because of that, we don't rely on repeated inducibility of electrophysiologic testing to gauge the efficacy of antiarrhythmic therapy in this group. This trial, this MADIT II trial was not designed to evaluate the utility of EP testing and I think it would be a corruption of these data to try and use them to decide whether or not the defibrillator works in the population in question. There was a trial that specifically asked that question and that was the MUSTT trial. The MUSTT randomized patients who had inducible tachycardia. It followed in a controlled fashion patients without inducible

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tachycardia and with inducible tachycardia, and showed that the risk of arrhythmic death and cardiac arrest, as well as total mortality, was significantly higher in the patients with inducible tachycardia.

The MUSTT investigators then published last November in circulation an article that was referred to earlier looking at the effect of the patients ejection fraction on outcome and compared that with inducibility. And what that analysis demonstrated very clearly was that both ejection fraction and inducibility contributed independently to total mortality. However, in the patients whose ejection fraction was less than 30 percent, the electrophysiologic test for those patients who had inducible tachycardia had higher event rates both for arrhythmic death and cardiac arrest, and total mortality than the non-inducibles. The differential was not nearly so striking as we observed in the patients whose ejection fraction was 30 to 40 percent.

So the electrophysiologic test does restratify, it's less accurate in patients with poor ventricular function, and that logically makes sense. The worse the LV function, the more the likelihood of heart failure and other factors that can cause a

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patient to die suddenly that we do not detect at electrophysiologic testing. The electrophysiologic test is not perfect, none of these tests that we have for risk stratification is perfect. It's not a simple issue. There are multiple ways to die

suddenly. The one thing that's clear is that the vast majority of these mechanisms for dying suddenly in this population are treated effectively by the defibrillator.

Dr. Sox: Thank you. Next is Dr. Holohan.

Dr. Holohan: This is a question for Dr. Moss. I'm on your page 23, which is the cumulative graph of shocks in patients during the study, cumulative probability of administration of shocks. And it's not surprising that this increases simply given the fact that if an event is possible, no matter how improbable, given enough time it will occur, anything possible will occur. The question I have is, we've talked about a cumulative probability of 40 percent at four years. How many actual patients of the total number in the trial were followed up to four years?

Dr. Moss: Well, it was rolling enrollment, and in the Kaplan-Meier curve in the New England Journal article, we started out with, say in

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the defibrillator group, 742 patients, and the denominator by one year was 503 patients, and by two years it was 274 patients, and three years it was 110 patients. And by four years, that is those who were followed for four years, were nine patients.

So that's why what Dr. Hall had said earlier, if you don't take into account time, you're comparing patients who may have only been followed for one month versus those who were followed for 48 months, and so you really have to adjust for the time exposure, it's a very important part of this. And what Dr. Hall said was that if you take a look at the two-year interval, or really 19 months, the average follow-up, it's about 20 percent, which is very close to the 19 percent that was quoted in the work of Dr. Goodman. So I mean, I think that's important in any trial where there is rolling enrollment, taking into account the time exposure is an essential part.

That's the way one also calculates the mortality and if you take the fact that you follow patients for four years but on average the patients were followed for two years, some longer, some shorter, that's where you get the differential mortality and it just gets larger. Now, I think you also have to take into account that the device itself

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has a longevity of six or seven years or more, and so one terminates a trial after an average follow-up of two years because that's when the mortality was shown to be significantly reduced, and we have the moral and ethical obligation to terminate a trial in patients who have agreed and signed up to be randomized when there is a clear differential survival benefit, and so that's the reason for a data safety monitoring board.

Dr. Holohan: I understand data safety monitoring. That wasn't the question I was getting at, thank you.

Dr. Redberg: Aren't the numbers actually on the bottom of that slide? It says there were five patients at year four on that slide, and 72 at year three. If you look at page 23, it says number of patients ICD, it starts out at 720 and then it goes to five at year four.

Dr. Holohan: You're correct.

Dr. Moss: Yes.

Dr. Sox: Does anybody else on the panel want to ask a question? We've basically got about seven more minutes before we're going to go to public comments. And you will have the opportunity to ask questions during our discussion after lunch, so I

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guess I will just, I probably should take them first from people who haven't already asked a question. Yes, please, Dr. Weil.

Dr. Weil: Yes. We had spent a lot of time so far talking about the various attempts to do a sustainability non-sustainability subgroup analysis, but I wanted to go back to the point that you, Dr. Moss, raised about the likely number of patients who would have met the MADIT I criteria in the patient population, and I think you came up with a figure of approximately 4 percent, and I would appreciate if if you or Dr. Hall could go a little bit further in explaining why you believe that that figure would not be sufficient to be explained by an overwhelming treatment effect for the inducible population as opposed to non-inducible population, because we had spent so much time on trying to get into the details of these particular analyses.

Dr. Moss: Well, if I understand your question properly, the 4 percent figure that we estimated is one thing, but it seems to me that what you're asking is could we account for the overall effect that we observed on the basis of inducible patients having a dramatic effect. Well, only 36 percent of the patients were inducible and 64 percent

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of the patients were not inducible, so it seems to be just in an overt way that there is no possibility that the inducible patients carried all of the weight of the trial, this is what this whole discussion is about.

Secondly, the indication and approval by CMS for MADIT I criteria are the ejection fraction, inducibility and non-suppressibility. Those were the criteria for enrollment. Those, any patient who was found to have -- with a non-sustained ventricular tachycardia. So you have to take into account those criteria, that was the criteria that was used for MADIT I. Okay? If you now say what are the percentage of patients who met, truly met MADIT I criteria, it's a very small percentage, 4 percent, 6 percent, 3 percent, I don't know. Also, it's not logical or possible that the mortality, overall total mortality reduction was carried by 36 percent of the patients in the ICD arm.

Dr. Sox: Dr. Wilkoff is next.

Dr. Wilkoff: I know this is a slightly different topic, but I want to get this information because I think it will come up later as well. My understanding is that approximately half the patients who got defibrillators had dual chamber

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defibrillators; is that correct?

Dr. Moss: It's not correct. About 80 percent had dual chamber.

Dr. Wilkoff: And do you have any information about the percentage of right ventricular pacing in the defibrillator group?

Dr. Moss: If I could just take a minute, I could give you the best information we have. 80 percent of the patients had dual chamber pacemakers.

In general the setting in the dual chamber pacemakers was in fact 70 beats per minute. If we look at the comparison of the dual chamber versus the single chamber, the 20 percent, the figures and the graphs, which I will be glad to show, look superimposable upon the DAVID study. No significant difference in mortality. More heart failure with a P value of about .02. The curves look very similar, although in the DAVID study all the patients had dual chamber and they were programmed to either single chamber at a backup pacing rate of 40, versus dual chamber pacing at 70. We do have percentage of ventricular pacing in both groups and we're just looking at that data now, but the overall -- and we have the graphs here and I would be glad to show them, are very very similar to DAVID.

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Dr. Wilkoff: Because it's interesting, and I don't know how this works out, but the mean in the non-inducible group, the data that Dr. Goodman showed us, showed that the mean heart rate was slightly increased, which suggests that there may have been an imbalance in the programming between the inducible and non-inducible group. And also as you said, the non-inducible group had more heart failure throughout this. So the question whether it is, not only was there possibly an imbalance between the heart rate but perhaps the percentage of right ventricular pacing between the inducible and non-inducible group, and so that's how, there's possibly another interaction that goes on with this.

Dr. Moss: Let me first say we're grateful for you and your research group in clarifying the issue of dual chamber and versus single chamber, effective single chamber, and we can only say that in a sense, you beat us to the punch, because the findings look very similar and I think your interpretations are good interpretations. And this is all retrospective. In any good study, you always find more information to carry out subsequent studies. If I remember correctly, the hypothesis of the DAVID study was the thought that the dual chamber

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might in fact do better, and it turned out that was not the case, one didn't appreciate desynchronization pacing, if you will.

And so like everything else, you design a study in 1997, and the study comes out, as you look over the data, it serves as very useful hypothesis generating study. Had you not done the DAVID study, we would have predicated, we would have wanted to look at that very carefully.

Dr. Wilkoff: Right. I guess the point I would make is it's not whether it's DDD pacing or VVI pacing, it's whether it's -- what is the percentage of right ventricular pacing. And when you do that analysis, I would like to see it at some point.

Dr. Moss: We do have preliminary data on that. There is no question that the dual chamber had something in the order of 92 percent time, where it paced the ventricle, and in the single chamber it was down around 12 percent, so we do have -- you can interrogate the device, which we did at close-out, and you can get the percent total ventricular pacing, and there is a huge difference between the single chamber and the dual chamber, in the range of around 10 or 12 percent in the single chamber and in the

range of 92 percent in the dual chamber, for
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ventricular pacing.
Dr. Sox: We're going to have one more question from Dr. Redberg, a brief comment from Dr. Goodman, and then we're going to hear from the scheduled presenters.
Dr. Redberg: My question is related to gender, because as you know, cardiovascular disease is the leading cause of death in women and in fact as we get older, there are more women than men with cardiovascular disease. But the MADIT trial population was only 15 percent women and in fact the confidence interval is plus one when you look at the data for women. And I look back at MADIT I and it was 8 percent women. So I'm wondering if there was some problem enrolling women in this trial or why the numbers are that low.
Dr. Moss: I can only say we were as proactive as we could to enroll women. I am pleased to say that the women appeared to get a better benefit from the defibrillator than the men, but in electrophysiologic testing and referral, I think whatever the bias is, I don't fully understand it at the present time, and I think the types of positions that you and associates are taking to try and expand this, we are contemplating a trial in the future to
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almost exclusively focus on women, because we don't think they have been adequately represented. But we did our best to enhance enrollment.
I think the same thing was probably true in the MUSTT trial and maybe Dr. Buxton would want to just comment on this. It's a difficult problem. Dr. Buxton, can we get at least a spontaneous comment?
Dr. Buxton: It's true that women relative to men were under representative and I think the percent of women in the trial, given the mean age of patients in the early 60s, is not that far off from the percent of women who have myocardial infarctions at younger ages.
Dr. Sox: Dr. Goodman, a brief comment, and then we will go on to hear from the public.
Dr. Goodman: I just wanted to state for the record, I was very chagrined to hear that there was a critical variable on pretrial inducibility testing that we might have missed. In fact, the miracle of modern computer technology allowed me to look at the data set that we were sent, and that variable is not there, so I don't know if it was in the original data set and not sent to us, I have no idea, but we have what looks like a complete data set
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but that variable doesn't exist.
One other point on the logic of our analysis and the issue of adjusting. We took advantage of the randomization in that if indeed the inducibility status was as we predicted, the assumption was that the various characteristics were randomly divided between the treatment group and the non-treatment group, and these sorts of adjustments are not necessarily done but when you're comparing two randomized groups they're certainly absolutely critical to be done when they are done within a single group, which was the analysis that Dr. Moss showed. So the two analyses are not working at cross

purposes here, they are analyzing in a sense two different things, because we were actually attempting to use inducibility status in the control group that they were not using in their analysis.

Dr. Sox: Thank you.

We are now going to hear from eight individuals who applied for the opportunity to speak before us. The ground rules are that you have five minutes to speak. And those of you who have been to these meetings know that I will cut you off if you go over, so please don't make me be impolite. The first speaker is Dr. Gregoratos, and I will remind him and

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the other speakers to state whether or not they have any financial involvement with manufactures of any products being discussed or with their competitors.

Dr. Gregoratos: Dr. Sox, Dr. Tunis, members of the panel, and staff, thank you for the opportunity to present you with the position of the American College of Cardiology, an organization of 28,000 physicians dedicated to the diagnosis and management of heart disease, an organization of which many of you on the panel belong.

I am Gabe Gregoratos. I'm a clinical cardiologist, not an electrophysiologist, at the University of California San Francisco. For the record, I have absolutely no connection, financial or otherwise, with any device manufacturer.

I would like to take a minute to discuss the guideline methodology of the ACC and the American Heart Association, since our guidelines have been mentioned many times this morning by several speakers. And the reason I am here is because I have been the chair of the guideline committee for the pacemakers and defibrillators since 1996.

The guideline process started in 1980 and it is interesting that the first published guideline was in fact one for pacemakers and defibrillators in

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1984. The motivation of the American College of Cardiology and the American Heart Association can be seen from this slide, and it's taken from the preamble of the first published guideline in 1984 and I read only part of it, but it says, it is therefore appropriate that the medical profession examine the impact of developing technology on the practice and cost of medical care.

Now I believe that our practice guideline methodology is quite rigorous. There is a parent task force from both organizations that appoints writing committees. Writing committees consist of general cardiologists, subspecialists and other individuals that are related to the subject at hand. The writing committee conducts extensive review of numerous databases. The draft guideline is exposed to an absolutely tremendous amount of peer review, and the peer review process is located on this slide.

As you can see, there are both internal and external reviewers from the ACC, the AHA. There are content reviewers. There are reviewers from other organizations. In the case of the current update, NASPE participated. It is rereviewed by the task force after the document has been modified, depending on the peer reviews. And I must tell you

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as an example that I had to respond to 27 peer reviews, many of which were multipage single spaced

extensive reviews of the document. So the document is extensively peer reviewed, revised, and then it goes back to the parent task force, approved and back to the parent organizations for a final vote before publication.

I would like to mention very briefly the classification of our recommendations, since that was mentioned before. Class IIa is a recommendation that pertains to conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness or efficacy of a procedure or treatment. But I point out the weight of evidence is in favor of usefulness or efficacy.

Most of this other information is in your handout. This is the membership of the committee that wrote the current update and the institutions and credentials of those members are listed in your handout.

So in my 58 seconds left, I will address question 2.a, which is the question on hand today. The answer to question 2.a as far as we are concerned, according to our guideline, is a qualified yes. The rationale for our recommendation in favor

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of prophylactic ICD implantation in the population of the MADIT II types is indeed the MADIT II trial, and you have heard all the data from Dr. Moss and I will not bother repeating it.

Our committee concluded that MADIT II is an important well-designed randomized controlled trial of seminal significance, and that MADIT II results do support the prophylactic use of ICD therapy in the subject population.

Now we have been asked, and you probably will want to ask me why did we assign this recommendation at IIa and not at Class I classification, and these are the questions that the committee had when it arrived at its IIa recommendation in June of 2002. I emphasize June of 2002 because since then, additional data have become available and I have no knowledge whether if we were reconsidering the recommendation today we would assign it a Class IIa or a different level recommendation. And you can see the questions that the committee had and you can read them on your own.

And I will, I have only one other thing, that we believe that it is inappropriate to carry out a comparison between MADIT II and the CABG Patch trial for all the reasons that were previously

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mentioned from this podium and the reasons that are listed in your handouts.

The position of the American College of Cardiology is as follows: We support the ICD therapy for MADIT II indications in this particular subject population. We recommend strict adherence to the MADIT II inclusion and exclusion criteria. We recommend continued investigation of optimum risk stratification of patients in this group. And we recommend development of a registry of patients receiving ICDs for MADIT II indications; the registry very importantly should include the date and method of LVEF measurement in relation to the date of myocardial infarction and/or date of revascularization.

I have additional data that I can provide you later on if you require.

Dr. Sox: Thank you very much, sir. I appreciate your efforts to try to stay within the time limit. We're now going to hear from Dr. Richard Cohen.

Dr. Cohen: Thank you very much. My name is Richard Cohen, and I am here to does microvolt T-wave Alternans testing, which is a noninvasive means of risk stratification of patients for risk of

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sudden cardiac death. By way of disclosure, this technology was developed in my laboratory at MIT. Dr. Joseph Smith and I were co-inventors of the technology, and MIT subsequently licensed the technology to Cambridge Heart. I have been involved with Cambridge Heart since its inception and I do have a financial interest in the company.

I would like to first present data from the multi-center regulatory trial which was done for the purposes of FDA clearance of this technology. In this study of patients undergoing electrophysiologic study at multiple centers, T-wave Alternans achieved a relative risk of 13.9 for prediction of ventricular tachyarrhythmia events plus total mortality. In comparison with invasive electrophysiologic testing, the event rate among patients who tested positive were comparable, about 25 percent. But the event rate among patients who tested negative was several times lower among the T-wave Alternans patients compared to the EP negative patients, accounting for the improved relative risk for T-wave Alternans compared to electrophysiologic testing, and this type of relationship between T-wave Alternans and EP has held up across multiple studies, and there's a table in your handout.

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The next study I would like to present is a study of 107 consecutive patients with Class II and III heart failure and no prior history of ventricular tachyarrhythmic events. Among patients who tested T-wave Alternans positive, at 18 months of follow-up, there was a 21 percent event rate. There were no events among the T-wave Alternans negative patients. And compared with six other noninvasive risk stratifiers, T-wave Alternans was the only statistically significant predictor.

The third study was a study from Japan of 850 consecutive post-MI patients. In this study T-wave Alternans achieved a relative risk of 11 and had an extraordinarily low event rate among patients who tested negative.

As has been previously discussed, the MADIT II trial was a prospective randomized trial, demonstrated a statistically significant reduction in mortality among patients who received ICDs. One of the clinical questions that has come up, as the previous speaker indicated, is the question of whether noninvasive risk stratification can be used to further refine clinical decision making and treatment of patients in the MADIT II group. I should point out that evaluation of risk stratifiers

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should properly be done in the context of trials designed specifically to evaluate prospectively a small number of risk stratifiers. Retrospective analysis of multiple clinical variables from preexisting studies and finding one that appears to work is fraught with statistical hazard.

I would like to present to you some data which was presented at CardioStim by Dr. Stephen Hanlauser, which is a subgroup analysis of the two previous studies that I showed you, the heart failure and myocardial infarction studies in patients not selected for preexisting ventricular tachyarrhythmias. 120 patients were identified from the two studies. All the original data was collected and the primary endpoint of the subgroup analysis was sudden cardiac death and resuscitated cardiac arrest. The secondary endpoint included nonlethal sustained ventricular tachycardia. Average follow-up was 17 months. Ejection fraction 25.6 percent. 28 percent of the patients tested negative, 59 percent positive, and 13 percent indeterminate. The Kaplan-Meier survival curves for primary events of sudden cardiac death and cardiac arrest are shown here. There was a 17 percent event rate among the positives, there were no events among the negatives. The result was

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statistically significant. For secondary events the relative risk was, which included nonlethal sustained VT, the survival curves are well separated with a relative risk of 5.5.

So in conclusion, T-wave Alternans, which is a noninvasive test, appears to compare favorably to electrophysiologic testing, it appears to be an effective risk stratifier for MADIT II patients, and appears to be a promising technique to identify which MADIT II patients are most likely to benefit from ICD therapy. Thank you.

Dr. Sox: Thank you, Dr. Cohen. We will now hear from Dr. Theodore Chow.

Dr. Chow: My name is Theodore Chow. I am a practicing electrophysiologist. By way of disclosure, I hold no financial interests in Cambridge Heart. I do receive research grant support from Medtronic.

Members of the committee, ladies and gentlemen, I would like to present to you the preliminary results of our T-wave Alternans testing program in MADIT II type patients as an elaboration of what you just heard from Dr. Cohen. This is a prospective trial conducted by a single large community based cardiology practice aimed at

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assessing the value of T-wave Alternans testing in patients with ischemic cardiomyopathy.

Since sudden death is the single most common cause of death in all cardiology practices, we have felt obliged to routinely assess risks in our patients. The strategies for risk assessment relevant to today's discussion are outlined on the left side of the slide. The merits and drawbacks of these approaches have been extensively discussed previously. I would also like to highlight that a Holter monitor is a poor predictor of risk, and this relates particularly to a MADIT I/MUSTT type approach but not to a MADIT II type approach.

Importantly, many patients without non-sustained VT may still be at high risk for sudden death even though they would be excluded from further evaluation according to a MADIT I/MUSTT type approach. Because T-wave Alternans have been shown to be predictive in a number of settings, we have incorporated this technology into our practice.

In our practice we have instituted a

program in which patients with CAD, an EF less than or equal to 40 percent, receive T-wave Alternans testing and Holter monitoring. EP studies and ICD implants are performed where clinically indicated.

We then follow patients for ventricular tachyarrhythmic events, which were defined as either sudden cardiac death, resuscitated cardiac arrest, or an appropriate ICD discharge for VT or VF.

There were 203 patients in our trial who met MADIT II criteria, of whom we successfully obtained follow-up on 193, or 95 percent. Patient demographics are shown here. The average patient was 65 years old, had an EF of 25 percent. 83 percent of patients were on beta-blockers, an important point because it illustrated that these patients were already being aggressively being treated medically for arrhythmias. 38 percent of patients received an ICD. Approximately 50 percent of patients tested were T-wave positive, 30 percent were T-wave negative, and 20 percent were T-wave indeterminate. The mean follow-up time was 375 days. There were 13 tachyarrhythmic events, comprising of nine sudden cardiac events and four appropriate ICD shocks. Nine events occurred in T-wave positive patients, one event was in a T-wave negative patient, and three events were in T-wave indeterminate patients.

This is a Kaplan-Meier curve illustrating freedom from ventricular tachyarrhythmic endpoints. You can see that there is a clear separation in the

curves, with T-wave positive patients having a significantly higher event rate with a P value of 0.035, and a relative risk of 6, at only 18 months of follow-up.

Based on these data, we constructed this screening algorithm in which MADIT II patients received T-wave testing. Clearly T-wave positive patients are at high risk and should receive ICDs. T-wave negative patients appear to be at lower risk and it may be reasonable to approach these patients more conservatively, although this still needs to be defined by a prospective randomized controlled trial. T-wave indeterminate patients have uncertain outcome and consequently, reasonable options would be to perform additional risk stratification using EP study or to proceed directly with ICD implantation.

In conclusion, then, I believe that these data suggest the following: Number one, T-wave Alternans testing is an effective noninvasive tool to evaluate MADIT II patients. MADIT II type patients who test T-wave positive are at high risk and should receive ICD therapy. MADIT II type patients who are T-wave negative appear to be at low risk and it may be reasonable to treat these patients conservatively, although again, this needs to be proven by

prospective randomized controlled trials. And then finally, MADIT II type patients who are T-wave indeterminate may be at high risk of tachyarrhythmic events, their outcome is uncertain, and either EP study or direct ICD implantation may be reasonable.

Thank you.

Dr. Sox: Thank you very much, Dr. Chow.

Our next speaker will be Mark Hlatky, from Stanford University.

Dr. Hlatky: My name is Mark Hlatky. I'm

a cardiologist from Stanford University, and I have no financial connection with any of the device companies here. I come to you as an interested researcher and from our large federally funded research grant where we looked at a number of issues related to ICD trials.

I wanted to summarize a couple of points about the evidence in areas where I think there are gaps. The first is that there are two kinds of randomized trials that are under consideration, prior ventricular arrhythmias and primary prevention type trials, and that the evidence here is a little different for these two different types of trials.

For the primary secondary prevention trials, AVID, CIDS and CASH have been pooled

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together, they are very consistent in their data showing a risk reduction due to ICD therapy, which applies equally to ischemic or non-ischemic patients, although there is evidence of heterogeneity according to ejection fraction, with more efficacy in the low EF group.

The primary prevention trials are different, however. These are the trials that have been completed to date, and the entry criteria are listed. And the main thing is that the entry criteria are quite different from one trial to another. The common denominator, however, is that they all require a low ejection fraction to get in. I put MUSTT in as a slightly different study because it is actually a trial of EP testing versus non-EP testing.

We did a meta-analysis of these trial results. I also want to point out that there are at least three, maybe more ongoing trials, including SCD-HEF, which has been mentioned, with over twice the size of MADIT II, and it has been continued by its DSMB and will be finishing in the fall.

The main point about the primary trials is that obviously there is a huge number of patients who are potentially eligible for these devices. The

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trials show significance, statistically significant evidence of heterogeneity of results, so that they are not consistent from one to another. All of them, however, share the characteristic that low EF patients were enrolled. The big difference is that they used different methods of risk stratification in addition to low EF.

The MUSTT study, which is a randomized trial of EP testing, showed better outcomes in EP managed patients.

As far as MADIT II is concerned, I think it has a high internal validity as a randomized trial, but the question is not about its internal validity as much as its generalizability. How much does this apply to all patients with a low EF who are post-MI in the Medicare group? I think as Dr. Moss said today, the screening for this group consisted of many many patients, and they actually don't know how all the patients were enrolled in the study. Some patients five years after MI were referred to electrophysiologists for reasons we don't really yet understand, and so I am not certain how well this group matches with the Medicare population.

Most importantly, there are a number of additional risk markers that have been collected in

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this group but not yet fully reported or analyzed. For instance, we just learned today about the EP testing done prior to randomization, which was not reported in the New England Journal paper, for instance. And I suspect that many other patients had additional risk markers, which is why they were referred for entry into the study. So I think the question is really whether this trial can be generalized to the Medicare population.

The final question that I would ask about this is the issue of sudden death stratification. This is an area we work on in our report study, and I think that there's 25 years of research that says that numerous factors in addition to ejection fraction predict cardiac risk. These include age, sex, and markers of ischemia, and the EP research world, including many of the investigators on the panel, have shown additional tests such as ejection fraction, non-sustained VT, signal average ECG, T-wave Alternans we just heard about, and patients at high risk of sudden death are those particularly likely to benefit from an ICD.

I think the big question is whether an EF below 30 percent in and of itself is sufficient to put in an ICD, and I would say that the question here

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is whether the evidence is adequate. I would say MADIT II is suggestive, it's highly suggestive, but it doesn't really prove the case completely for this. The word that was used earlier by Dr. Moss and the representative of the company was a paradigm shift, a paradigm shift to say that we don't need any additional markers of patients with low EF. And I question that because this is a single study, it's very well done, but it's only a single study. And I think we have 25 years of research that says that there are other markers that are important and for that reason I am concerned that an indication from Medicare that says that ejection fraction alone is necessary to put in an ICD is overly broad, and would expose many patients who would not benefit from this device to risks, to say nothing of the large cost to the program. Thank you.

Dr. Sox: Thank you Dr. Hlatky. The next speaker will be Dr. Bruce Lindsay.

Dr. Lindsay: Thank you. I direct the electrophysiology laboratory at Washington University, and I'm here to represent NASPE. Our mission is to improve the care of patients by promoting research, education and healthcare policy.

This slide summarizes some of the data

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from the secondary prevention trials, AVID, CASH and CIDS, which looks at mortality rates per year between the outcomes in patients with ICDs. One of the things that has been reported in CIDS is that when they looked at the data this year, they found that over time there was a wider separation between the ICD and the amiodarone groups; that was presented at the American Heart.

In the meta-analysis, there are a couple of numbers that I want you to try to remember. The relative reduction in total mortality was 27 percent, and for arrhythmic deaths, 51 percent. I mention this because in total mortality, that relative reduction is not too much different than the studies

we will be referring to later. The ICD therapy was preferred over drug therapy in their conclusions, and especially in those with moderate to severe LV dysfunction.

What brings us here today are the primary prevention trials, and you can see here some of the mortalities, both in the absolute reduction and relative reduction in these trials. In the MUSTT trial the numbers in parentheses are at two years and the other numbers are at five years. What we're really focusing on today is the data that I have

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highlighted in yellow for the MADIT II trial, where the absolute reduction was 5.6 percent and a relative reduction of 31 percent, and that relative reduction is really not much different than some of the secondary prevention trials. But because it's lower in magnitude than the other studies, it's attracted some attention as to whether there are better ways of analyzing the subgroups.

We have been through that earlier on today and the analysis has not shown any particular subgroup that is especially prone to benefit from an ICD. And I agree with Dr. Buxton's comment that this study is simply not designed to look at the merits of EP studies.

Now a question arose as to whether new or worsened CF heart failure should restrict ICD use, and I think this was raised because of some trends observed in MADIT II and DAVID. We shouldn't lose the forest through the trees, and that is that MADIT II does reduce mortality. The companion trial was stopped this year because ICDs improved survival. There's some evidence from a German group that looked at the impact of ICDs on patients awaiting cardiac transplant, and it improved survival because it virtually eliminated sudden death. And then when you

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look at the secondary prevention trials, certainly the benefit is greatest in those with the lowest EFs.

So the conclusions I would come to is that the patients with severe LV dysfunction are the ones most likely to benefit from ICDs. Heart failure may influence the model of the ICD or the way it's programmed, but these are decisions that should be made by physicians with expertise in the management of patients with VT or VF.

I would like to focus now on some of the data from MUSTT, and this is taken from the group that wasn't treated. The upper curve, which is the group at highest risk, was the low EF inducible group; the third curve down was the higher EF inducible group; and in between are those who had a low EF and non-inducible. So the question I would pose to you is why would you implant a defibrillator in the highest curve and the third curve, but not the one in the middle.

Maybe you'd say well, they don't have the arrhythmic deaths. But in fact when you look at the arrhythmic death rates in these patients, again, the highest is the low EF group that was inducible, the third group down is the high EF that was inducible, but the low EF that was not inducible is superimposed

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on the third group. So how can we develop a policy that would implant a defibrillator in one group and not the other when in fact the risk is the same.

These summarize the event rates. Again, the numbers in yellow represent the high risk group because they have low EFs, but if you look at the low EF negative induction compared to the higher EF positive induction, they have the same arrhythmic mortality. So I don't see how we can develop a policy that would implant a defibrillator in one group but not the other.

So our conclusion from the primary prevention trials is that there's about a 31 to 54 percent relative reduction in mortality by ICDs. I would recommend EP studies to stratify risks in patients with an EF of 30 to 40 percent, but I don't think they should be a prerequisite for ICD therapy in patients with an EF of less than 30 percent.

And the recommendation from NASPE is that CMS should extend coverage for ICD therapy to patients who fulfill MADIT II criteria. We also felt, as has been discussed earlier in the day, that there are other techniques that may improve risk stratification and this needs to be looked at as more data becomes available. Thank you.

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Dr. Sox: Dr. Lindsay, could you just tell us about any financial relationships you might have?

Dr. Lindsay: Oh, I'm sorry, I meant to mention that. I have absolutely no conflict of interests or ties to any of these companies.

Dr. Sox: Thank you. Our next speaker is Dr. David Cannom.

Dr. Cannom: Thank you, Dr. Sox. Good morning, members and guests. I am here representing the practicing physician, as well as one who has the good fortune because I have been involved in these clinical trials, to see the evolution over the last decade of the set of randomized trials that we have been discussing today, and I therefore have two concerns. One is, a no vote today would inhibit my ability to take appropriate care of my patients. And secondly, I think it would have a devastating effect on the future of clinical trials in this country.

I am a member of the Guidant MAB and I was asked to come to speak today by Medtronic. The era of clinical trials, for those of you who didn't work your way through it, is really an extraordinary one, and began in 1990 at a time when the ICD was really not a prominent part of clinical practice. We were relying on much physiologic studies and suppression

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with antiarrhythmic drugs. No secondary prevention trials had been started or completed. There were prominent electrophysiologists who thought that randomized trial with the ICD were, frankly, unethical and shouldn't be done.

But, I think the wisdom in the field prevailed and we did initiate a series of trials, first in the secondary group and then in the primary group, that had important implications for us as clinicians and scientists, but also had very important cost implications.

You have heard about AVID, CIDS and CASH. I'm not going to go over those, only to say that the reduction in total mortality shown in yellow here in was similar in these three trials and interestingly enough, was not as marked as that reduction in the primary prevention trials.

You've also heard as much, or maybe more

than you want to hear about MADIT, MUSTT and MADIT II, but one point has not been emphasized yet, and that is that there were significant treatment differences in these trials. Back in the MADIT I era, 1994-95, we were not using beta-blocker and ACE inhibitors in the same aggressive way that we do now. And in MADIT II, shown on the right, we achieved a 70

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percent use of beta-blockers and ACE inhibitors, which I think accounts for some of the differences in the mortality curves that you saw between those two trials.

Just to put some human touch around what a MADIT II patient looks like, this is one of our MADIT II patients in the trial, a 70-year old Latino female who had had a large anterior wall infarct in 1998, was bypassed. Her EF was 20 percent. She had multiple admissions for heart failure, was diabetic. She had a narrow QRS. She was enrolled in MADIT II in February of 1999. She did have a post-procedure EPS and was non-inducible, and went on to have two true shocks in July and August of 2000, and is currently doing well. And shown on the upper panel are the play-outs from the ICD at the time of her defibrillation. So this is one of the 134 patients to which Dr. Moss referred that survived because of her enrollment in MADIT II and her reception of an ICD.

The risk reduction in the primary prevention trials, as I said, has been higher than that in the secondary prevention trials, I think a fact that surprises us a bit, but has held consistent across all the trials.

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So what conclusions does this aging clinician come to about the data that we've seen today? Certainly going back to AVID, CASH and CIDS, the existing evidence for current indications is compelling, it's used on a daily basis, and it certainly has become the standard of care.

Broadening coverage in the primary prevention group based on the MADIT II data that we've heard today, I think has at least four implications. It will bring life-saving therapy to Medicare patients who are eligible using MADIT II criteria and what Dr. Moss and the executive committee of MADIT II thought was a very simple entry point, but clearly it is not as simple as we thought it was. We'll strengthen reliance on evidence-based medicine and clinical decision making. This was not true a decade ago, but is true now. We will increase reliance on specially generated practice guidelines. I don't know how we can in good conscience not agree with what NASPE, the ACC and AHA think is true about patient care. And I think deeply importantly, it will encourage the design and completion of further well done clinical trials that will help clarify some of the points of discussion made today. Thank you.

Dr. Sox: Thank you very much, Dr. Cannom.

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We will now hear from Dr. John Boehmer.

Dr. Boehmer: Thank you, Dr. Sox, members of the panel. I come as a heart failure cardiologist, one who takes care of a great number of patients with low ejection fraction. I am a heart failure cardiologist from Penn State College of Medicine, Hershey, Pennsylvania. I have been

involved in clinical trials, some of which have been funded by Guidant and Medtronic. My work involves the care of a great number of patients with heart failure.

As is well established, heart failure patients frequently suffer sudden death. I have much more personal experience with these tragic events than most physicians. As a result, I became involved in several clinical trials to prevent sudden death in heart failure. These include the Sudden Cardiac Death and Heart Failure Trial, in which I'm an investigator and events committee member; the Contact CD trial, in which I was an investigator and events committee member; and the Companion trial, in which I was an investigator and on the steering committee.

Prophylactic ICDs have not gained wide acceptance in the heart failure community. The reasons are complex, but include challenges in

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patient identification and barriers to therapy. Both the MADIT and MUSTT studies included the presence of ventricular arrhythmias in electrophysiologic study to meet the entry criteria. Clinically, this translates to the need to screen for arrhythmia, presumably with an ambulatory ECG monitor, and then refer those who had non-sustained ventricular tachycardia to an electrophysiologist for further study. In our community, this is not a terribly common practice.

In the most recent ACC/AHA guidelines published 14 months ago, the only indication for ICD therapy was judged to be those who have had sudden death ventricular fibrillation or hemodynamically destabilizing ventricular tachycardia. Any prophylactic indication was listed as Class III, and routine Holter monitor was likewise listed as Class III. I think this is going to change with the data as it comes to bear.

The heart failure community had concerns about MADIT and MUSTT trials. The MADIT trial was complicated by small numbers and imbalance of medical therapy, particularly with beta-blockers being more commonly used in the ICD groups, and the heart failure community is very fond of beta-blockers. The

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MUSTT study was impressive in the magnitude of benefit of ICDs; unfortunately, there was no prospective hypothesis that ICD therapy would have led to the benefit, therefore, introducing possibly selection bias. Taken together, the heart failure community did not move towards aggressive use of the monitoring for arrhythmia or frequent referral for electrophysiologic testing.

The MADIT II study was the first to use prophylactic ICDs in a patient identified by their history of myocardial infarction and LY systolic function. Importantly, there were no arrhythmia criteria used in making this decision, making it largely a trial of LV systolic dysfunction.

The study was well designed with a clear prospective hypothesis that ICD therapy would improve all cause mortality, the groups were well treated and well balanced, the termination of the study was prospectively described and the stopping rule was followed, and the study was stopped during active enrollment when a statistically significant survival advantage was detected in the population as a whole.

However, because of the methodology and the findings that were presented today, there were no subgroups that appeared to benefit more.

Concern has been raised about using this type of therapy to alter the mode of death from one of sudden death to one of greater morbidity associated with worsening heart failure. Although it is true that the incidents of sudden death in heart failure populations is lower in those treated with ICDs, and the incidence of progressive heart failure then becomes more common, this decision belongs to the patients. Patients can elect the risk of sudden death and not to have an ICD, of they can elect to have the ICD and prevent sudden death. The decision is not irrevocable and patients can alter that decision by having the defibrillator programmed to off. In my experience, many patients opt to have ICD therapy when presented with this option, even though they have heart failure, many of which are very symptomatic.

Our present situation is one of recognizing high risk patients, understanding the data as they currently exist, and coming to our best decision of what we believe is in our patients best interests. To illustrate the point, a Catholic priest was recently referred to me for evaluation of his condition. He is a 57-year old man who suffered a large anterior myocardial infarction in 1999

complicated by congestive heart failure. He stabilized and is now functional Class II, appropriately treated with beta-blockers, an angina-tension receptor blockers, diuretics and Digoxin. He has no significant comorbid illnesses. He has a dilated ventricle and ejection fraction of 20 percent on echocardiography. He has no history of ventricular arrhythmias and has been monitored in the hospital following his myocardial infarction, as well as more recently by ambulatory ECG monitoring. He has no ventricular arrhythmias demonstrated.

Do I recommend an ICD for him? The data are compelling that he is at risk for sudden death. Will his insurance pay for it? He has private insurance but they have elected to follow the lead of CMS. Do I recommend what I believe is best for the patient, specifically implantation of an ICD, despite the lack of reimbursement, or do I not? We need the leadership of CMS on this issue. Although the heart failure community has not endorsed prophylactic ICD therapy, I think the data are now becoming compelling and I think this will change in the very near future.

Dr. Sox: Thank you, Dr. Boehmer. Before you leave the podium, could you just clarify whether you have any financial relationships with any device

manufacturer?

Dr. Boehmer: The only financial relationship is as an investigator in clinical trials performed by, sponsored by Guidant, and SCD-HEF trials sponsored by the NIH and Medtronic.

Dr. Sox: Thank you. Our next speaker is Dr. Joanne Lynn.

Dr. Lynn: I also have no financial conflict of interest. Implantable cardioverter defibrillators can dramatically change the experience of the last phase of life for worse as well as for

better for a great many people at a very large cost. This committee and the society generally should take this opportunity to learn how to handle the dissemination of very costly treatments, whose usefulness varies dramatically in different populations, especially when those treatments may well be applied mostly to people who are inexorably coming to the end of life and suffering from frailty, progressive disabilities and organ system failure. Specifically, we could set in motion processes that would teach us how to assess the complex merits of treatments that will heavily be used in the last few years of life, for patients with substantial coexisting illness. How to insure that patients and

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their families can make thoughtful and informed choices about these treatments. And how to consider responsibly the merits of alternative strategies for the use of caring for patients with eventual fatal illnesses.

You should know some of the kinds of issues of ICDs that have come to my attention as a practitioner in long-term hospice nursing home care. Hospice providers talk of dying people whose last days were marred by repeated electrical discharges, often proceeding until the batteries were exhausted. Under some interpretations of the law, a demented patient must have an ICD when it would otherwise have been used in a patient without dementia, and these nursing home patients are eligible as well. Patients and families encounter barriers when they try to stop an ICD because the patient faces a more difficult dying with an alternative cause of death.

These situations and the limited literature concerning the use of ICDs in patients of advanced years with serious frailty and comorbidities point up three important and potentially true claims about ICD use. Some patients might not gain a longer life span either because the device is ineffective in their circumstance or because the patient dies more

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quickly as a result of another illness. Some patients might gain a longer life span but would have so many adverse effects, for example from worsening heart failure, during the prolonged life as to have on balance no advantage. Some patients might gain an increased life span without major detriment to the quality of life, but the gains would be so small, the cost so substantial that the use of ICDs will widely be seen as unfortunate and imprudent.

This committee should call for the collection of data needed to determine whether these claims are true, and Medicare should cover ICDs only for clinical situations where good evidence shows that ICDs actually improve lives for patients in these circumstances. Mostly, this we do not know. Most studies of ICDs require having been referred to the study, being able to come to the treatment center, having no dementia, having no serious comorbidities, being able to follow directions and giving informed consent to the study. Most have even required being younger than 80, which incidentally, disproportionately excludes women. Criteria like these has the unnoticed side effect of excluding very old, frail and otherwise sick people, even though these are the kinds of patients who well make up most

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of the Medicare population that is eligible for ICDs.
You cannot generalize to most sick Medicare patients because no one has studied them. Some patients may have much worsened symptoms from their heart disease as well as anxiety, life disruption and other adverse effects from ICD discharges. Half of people who live past 85 years of age will have substantial dementia; these patients have not been studied. Many cardiologists, I've asked many cardiologists about consent to ICD. So far only one document that I have seen tells people that they will still die and that before they die, they will want their ICD disconnected. We are not giving people honest opportunity for consent on the guide to ICDs.

Finally, ICDs provide the opportunity to learn how to respond to the issues created by very high costs. If a person lives just a few years with an ICD, the average added cost would be around $100,000. MADIT II criteria would provide an ICD for around a fifth of all Americans over their lifetime. This one device could cost Medicare $20 billion per year. No new treatment before this raises this kind of cost concern for Medicare. Raising the cost for the last phase of live by 50 percent may well be

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unsupportable and gender divisive disparities create overwhelming hardships for families and taxpayers, and undercut the general support of Medicare.

Most of the potential use is in patients of advanced years, with substantial comorbidities and more than one potential cause of death. We really must pause to consider appropriate care for this part of our lives. Many of my elderly patients find it unintelligible that they should be able to get any surgery or device that might extend life but they cannot get reliable nursing aide assistance, medication for pain, or support for family caregivers.

In sum, I would recommend that the Medicare Coverage Advisory Committee do the following:

First, advise CMS to issue a national coverage determination for ICDs only for the populations where evidence is strong that they actually gain desired outcomes, which may mean that only a very small part of the Medicare population should be covered now, and certainly does not now include elderly who have multiple comorbidities and competing causes of death.

Second, we should call on CMS to insure

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that Medicare patients have a high standard of informed consent. We should recommend that CMS institute methods to monitor outcomes, that they require evidence about all of the outcomes, including quality of life. That they monitor changes in the performance over time, and call on various parties to take up discussion of the priorities and values that are at stake.

Dr. Sox: Thank you. Well, before we take a lunch break, I would just like to ask the members of the panel to be thinking about a few key issues that we need to be discussing once we get to the discussion period in order to form a decision about whether the evidence is adequate that ICDs are effective. So at the risk of encouraging you to

develop indigestion during lunch, I ask you to nonetheless try hard. And we will see you back here at seven minutes after one.

(Luncheon recess.)

Dr. Sox: We're going to resume the meeting at this point and the first subject is open public comments. We've heard from about a dozen people that they would like to address the panel. Because we only have a limited amount of time to do this, the people who wish to address the panel are

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going to have to confine their remarks to one minute, 60 seconds, and that should include a very brief statement about financial connections, because that's important we do that, to be fair to everyone. Because we are going to limit the time to the 20 minutes allotted for this, I really do ask that you in the spirit of fair play, to keep it brief, one minute.

So, what we're going to ask the people who wish to speak is to line up at the microphones now. This is it. We prefer that nobody else get up. If you're going to get up, get up now. Okay, so we will go from one side to the other. Please identify yourself, state any financial conflicts, and then speak for a minute. Sir, would you start please?

Dr. Higgins: My name is Steven Higgins. I'm an electrophysiologist from Scripps in La Jolla. I am on the medical advisory board for Guidant but have no financial conflicts. I would like to address this to the voting members because we have been distracted for a long time today talking about subtleties of the different aspects of the study and kind of gotten away from the basic science, which is pretty bulletproof in the study, pretty clear-cut. I don't think there is much debate there and I'm a

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little surprised we are here.

But let me put this in perspective just to tell you about a patient I just recently saw. I had this nice 56-year old Afghani immigrant who came here 20 years ago, started working at a video store, raised a daughter who is now in UCLA in college, and then suffered a big MI and went on disability, went on Medicare and MediCal for the past ten years. We was cared for by an excellent heart failure doctor who had him on six drugs, and sent him to an electrophysiologist at his center.

Dr. Sox: About ten seconds.

Dr. Higgins: Thank you. And he recommended that he have a defibrillator. But for some reason it was delayed for two months, and the day before he was scheduled to have his surgery, he was down at UCSD medical school, with his daughter who was interviewing, and he died suddenly.

Dr. Sox: Thank you. Now we'll go to this microphone.

Dr. Strobeck: Good afternoon. My name is Dr. John Strobeck. I'm a practicing cardiologist, currently treasurer and chairman of the Heart Failure Society of America. The Heart Failure Society is extremely delighted to present some material and

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agrees that sudden cardiac death is a major cause of death, both primary and secondary prevention needs to be considered. Its comprehensive practice guideline, which is a data driven guideline, now currently

recommends that ICD implantation using the MADIT criteria has proven validity with evidence that's comparable to the ACC/AHA/NASPE guideline strength of evidence.

The Heart Failure Society guidelines are a living document that are expanded as necessary to include the results of new randomized clinical trial data, especially those that are in the progress and probably will deal with patients of more severe symptoms of heart failure as well as those suffering from more severe coexisting comorbid diseases.

Dr. Sox: Thank you, sir.

Dr. Berger: I'm Ron Berger. I'm en electrophysiologist at Johns Hopkins, here in town. I've consulted for Guidant in the past and have no financial conflicts of interest.

I want to very quickly amplify and summarize a couple of observations from this morning. First of all, this is a well designed randomized controlled trial with a very clear positive result and we shouldn't lose focus on that.

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Secondly, if we look narrowly at non-inducible versus inducible patients, as I heard the data this morning, there is now a subanalysis that's available that was confined to patients who are non-inducible based on prerandomization studies that had a number of patients larger than in MADIT I. As I understood, it was 257 patients, 144 in the ICD arm, 113 in the control arm, with a result that was quite clear, that ICDs were beneficial, even in these non-inducible patients.

I want to point out that we as an EP community have taught, as Dr. Redberg had suggested, that EP studies are supposed to be useful as a risk stratifier. I think the new data that we're learning is challenging that concept and we should realize that.

And finally, I want to point out that just because a risk stratifier may segregate patients in outcomes, it doesn't mean that it will identify patients who will benefit from a certain therapy. And this particular study, the MADIT II study, examining one risk stratifier, ejection fraction, had a highly significant result.

Dr. Sox: Thank you.

Dr. Buther: Greg Buther, from San

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Antonio, Texas, practicing electrophysiologist. I own a small amount of stock in Guidant and Medtronic both.

A no vote today by the committee means that when I go back to work tomorrow and am faced with a MADIT II patient, you're asking me to ignore the results of a landmark study published in the New England Journal and halted early, ignore my own clinical experience, ignore the recommendations of the ACC, the NHA and NASPE. Why? Because there may exist a small subgroup of these patients for which there is no benefit. This is unproven so far.

Maybe there is a subgroup that does not benefit and maybe my patient that I'm going to see tomorrow is lucky enough to be in it. On the other hand in the meantime while we work this out, those patients who aren't so lucky as to be in that unidentified subgroup are going to die just as MADIT II says they will.

Dr. Sox: Thank you.
Dr. Fellows: My name is Chris Fellows. I'm a practicing cardiologist and electrophysiologist from Seattle. I have no financial ties. My institution does receive support for research from all three companies.

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My comment's about evidence based medicine. We have been taught, I have been in practice almost 20 years, and when I started we were not evidence based. Now we are pushing more and more and more to do evidence based medicine. For instance, in 1997 the CABG Patch study came out and before that we were putting patches in everybody with a bad heart that went CABG because we knew they were at risk of dying because they had a bad heart. We don't do that anymore. We haven't done that since 1997.

Now we have another landmark study that comes out and says this is a clear-cut 31 percent reduction in mortality in this group of patients. All of the guidelines that I have to face every day tell me to put this in. I need to be able to put this in all the patients. I can't segregate them out into two groups. I think it's very important that we have a yes vote. Thank you.

Dr. Sox: Thank you.
Dr. Weiss: Daniel Weiss, practicing electrophysiologist in South Florida. I have a small amount of stock in the major companies and I have done some ad hoc consulting. I have no other financial interests.

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I think that one of the questions that I think at least the physicians on the panel need to ask themselves, the same question that Dr. Buther said we need to ask ourselves. You're going to go home tomorrow. What are you going to tell your patient with a low EF, when you have all this data? Even the people who detracted from the trial in the sense that they thought there might be some subgroups that would not necessarily benefit, agreed that the trial was well done. It's a large well done randomized control trial. That is our gold standard. And to go home now and tell our patients I'm sorry, I know that for every other thing I've recommended to you, I've told you I'd done it based upon the trials, this time I have to say you can't. Why, I don't know, the committee said no. How are you going to explain that to your patients? And if you can tell me, then you can tell me what I can tell to mine tomorrow.

Dr. Sox: Thank you. Yes, sir?
Dr. Gullum: I'm Francis Roosevelt Gullum. I'm in Richmond. I'm headquartered at Duke University and am an electrophysiologist.

I just wanted to emphasize something Dr. Berger said because it was stated this morning as

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well. The electrophysiology as a risk stratifier may be helpful at determining which patients may have ventricular tachycardia. It does not, however, predict which patients are at risk for sudden cardiac death. That is the thing that, we would love to have that glass to look into the future and see that. But when I look in the eyes of my patients, I have no way to measure which ones are going to drop dead, which

ones are going to have ventricular tachycardia.
The EP study can help me predict who might have monomorphic ventricular tachycardia. It cannot help me predict who is going to drop dead suddenly. This study allows us to identify a very small subset of those people who are going to drop dead this year. The vast majority of the people don't have, if you will, the good fortune of having a bad heart and a history of heart attack and a bad EF to help us identify them. They're going along their merry way until they just drop dead. Thank you.

Dr. Sox: Thank you.

Dr. Zimmerman: John Zimmerman, Hackensack Medical Center. I'm an electrophysiologist. I just want to emphasize that we now have a study showing a 31 percent reduction in mortality in people with EF less than 30 percent. It has been approved by the

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ACC, AHA, FDA has approved it. Some healthcare, Aetna, Blue Cross Blue Shield has approved. If you do not approve, if CMS does not approve the study, we are going to potentially have two healthcare systems in this country, we're going to have people that we can put it in, people that we can't put it in, and I think that's a very dangerous precedent to set.

Dr. Sox: Thank you.

Dr. Algafib. I'm Senna Algafib. I'm a cardiac electrophysiologist at Duke University and I have a master's degree in clinical research, and I have some experience designing and running clinical trials.

In reviewing the MADIT II paper, I see no issues at all with the design and the conduct of the trial, nor do I see any problems with the analysis of the data. Actually, I was surprised that the main focus of the discussion this morning was on subgroup analyses when prominent statisticians such as Dr. Lee taught me that subgroup analyses at best help us like generate hypotheses, but you can never draw definitive conclusions based on subgroup analyses.

And if you ask me, if I meet the MADIT II criteria, or a family member of mine meets the MADIT II criteria tomorrow, would I implant an ICD in

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them, my answer is an absolute yes.

Dr. Sox: Thank you.

Dr. Stein: Kent Stein, an electrophysiologist at Cornell. I've participated in industry sponsored research from all the major manufacturers, no other conflicts.

I just want to reemphasize that this is a large trial, but not as large as it was designed to be because it was terminated prematurely by its DSMB because it would have been unethical to have continued to randomize people to conventional therapy. In that setting, to focus on post hoc nonrandomized subgroup analysis is to commit statistical homicide. The evidence is overwhelming that the population as a whole benefits. There is not adequate evidence for you as a committee to conclude that that benefit is confined to the inducible subgroup. My patients know that they are at risk of sudden death, they know that their lives can be saved by defibrillators, they want defibrillators and their government ought to pay for it if they're Medicare beneficiaries.

Dr. Sox: Statistical homicide?

Dr. Martin: I'm David Martin, a clinical electrophysiologist at the Cleveland Clinic. I've worked with industry sponsored research from all the device manufacturers.

I would like the panel members to put themselves in my patients' place. An EF 30 percent or less, previous MI, and I recommend an EP study because right now we have to do it, and they ask me if it's better to be inducible or non-inducible. If you're inducible, you're going to get the defibrillator. If you're non-inducible, you're not going to get a defibrillator.

All the data from MADIT II, MUSTT, all the data are consistent. You live longer. I did an analysis from our EP database. If you're inducible, you live longer. All those patients got ICDs. If you're non-inducible, you don't get an ICD, those patients had higher mortality. Thanks.

Dr. Sox: Thank you. Well, that ends the period for public comment. The committee can ask questions of you, but according to the rules of the game, you have had your shot at identifying, addressing us except under sort of our rules.

We're now going to proceed to the discussion period, and I'm going to stand up. Can you turn this thing on? Well, now is the time when we really kind of work as a group, we try to ignore those folks out there and work toward a conclusion and a vote.

I'm going to start off by addressing the voting panel and ask them a question about the procedure which, I am going to make a proposal and so, this is our second voting question, but it's really the important one for us so we're going to focus our attention on that. If you read that question, you see that there really are two questions contained within it. One is, is the evidence adequate to draw conclusions about the net health outcomes, which are based on the studies that we have been discussing this morning. And then the other question embedded in that is the question about applicability to Medicare patients.

In the MCAC sort of operating rules, we have been taught to first of all deal with questions of internal validity. Is the evidence adequate to judge effectiveness in the studies that are available in the public record? And the second question is, is the evidence adequate to judge the applicability of the findings to all Medicare patients, in this case with a reduced ejection fraction and a prior MI.

I think it's going to be easier for us, and I'm now speaking to the voting panel, to effectively divide this question and to focus on first of all the question about whether the studies that we have been presented, which really amount to the MADIT II trial, have proved that the use of ICDs are effective in the study population. And that's going to involve a fair amount of discussion, I think, about whether it's desirable, appropriate or not, to divide the population into inducible and non-inducible patients, and then actually discuss that, take a vote on whether we believe that in that population of patients defined by those inclusion and exclusion criteria, ICDs are effective.

We then move on, I propose, to the second question which is, is the evidence adequate to judge the applicability of findings to use in Medicare beneficiaries in general, and again, it would be Medicare beneficiaries with a low ejection fraction and post-MI. I think we'll do a lot better if we try to divide that question instead of trying to deal with it and vote with it all of a piece.

So, my question to again, the voting panel, the people who are going actually going to vote is, how do you feel about dividing the question? Is there anybody who would like to object, that's probably the quickest way to get to it. There are no

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objections, so we will then rephrase the question, the two voting questions so that they match up with the division of the question. We will also apply this technique to the first voting question, but we're going to spend most of the time on the second voting question since the first voting question is about a patient population for whom CMS already covers the ICDs.

I'll make a suggestion about how to rephrase this, since I'm the editor, and unfortunately even in my real job my word is not law, but I will suggest that we say, is the evidence adequate to draw conclusions about the net health outcomes in something like Medicare age patients meeting the exclusion and inclusion criteria for the clinical trials? Does that sound reasonable?

So Medicare age patients, I would say who meet the inclusion and exclusion criteria for the MADIT II trial.

Dr. Curtis: Aren't you really saying exactly the same thing but just rewording it?

Dr. Sox: Beg your pardon?

Dr. Curtis: It looks to me like you're saying exactly what the original question was, only just using different words.

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Dr. Sox: Well, no. We're changing it from all Medicare patients to Medicare age patients who meet the inclusion and exclusion criteria for the MADIT II trial.

Dr. Curtis: Well, originally it said Medicare patients with a prior MI, LV et cetera, et cetera, will are the inclusion criteria for MADIT II.

Dr. Sox: Well, that's the inclusion criteria but it doesn't include the exclusion criteria, for example, patients who have a serious illness and may die within two years of randomization.

Let's look at that top paragraph and see if it does it. Maybe we need to say as primary prevention for sudden cardiac death, add that here. So, does that top paragraph do it? Okay? So we can delete the second bullet now.

Dr. Carlson: Dr. Sox, one of the exclusion criteria from MADIT II was a MADIT I indication.

Dr. Holohan: Prior to enrollment.

Dr. Carlson: I just wondered if you get yourself into a circular, and maybe we should say other than MADIT I.

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Dr. Sox: So you're suggesting other than

the MADIT I criteria, since they already cover that?
Dr. Carlson: Yeah.
Dr. Sox: That's a good qualifier. Any other comments or concerns? Rita.
Dr. Redberg: Why would we just not use the inclusion and exclusion that are listed for the trial?
Dr. Sox: Beg your pardon?
Dr. Redberg: Why not just use the exclusion and inclusion that are listed here for the trial?
Dr. Sox: Well, mark has raised the question about whether the MADIT I criteria, whether you then get into a circular argument. You guys are going to, electrophysiologists have got to help us general internists out on that one.
Dr. Curtis: You know MADIT I patients, that's covered already, we know that. I think what we want the question to say is if you have a MADIT II patient, is the evidence sufficient? So I don't -- I mean, you could qualify it and say who don't have a Class I indication for an ICD, who don't meet MADIT I. I mean, we all know that.
Dr. Sox: So you think the qualification

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is unnecessary?
Dr. Curtis: I do, yeah.
Dr. Sox: Reasonable, Mark? Okay, let's take it out. So then in the second line I think we want to say something like, if yes, is the evidence adequate to apply the findings of the MADIT II trial to all Medicare patients who meet the inclusion criteria for the MADIT II trial. Let's see what you guys think. Rita, what do you think?
Dr. Redberg: I think it probably means about the same thing, so whatever is fine.
Dr. Sox: Okay. So we reframed the question, divided it really in two and we can still fuss with the wording, but at least I think we have gotten to a point where we can now discuss the divided question. Dr. Krist?
Dr. Krist: Just as a clarification, I mean, our purpose here that we're trying to with the first part address the internal validity, and the second part the external validity?
Dr. Sox: Basically, yeah.
Dr. Krist: Because there's still other components of internal, or -- the first one the way it's worded isn't just internal validity because there's also components, it's not just that they meet

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inclusion or exclusion criteria, it's also is the population that was referred similar and those type of aspects. Are we supposed to be addressing that with the first one, referral by -- beyond the exclusion and inclusion criteria.
Dr. Sox: I think the issues about how you assemble the cohort of patients for the study, those probably deal mostly with the second question.
Dr. Krist: So that's where we want to focus then, okay.
Dr. Sox: So I would like now to suggest that we begin the discussion of the second question, and I would like to hear suggestions about things that we ought to talk about with respect to the first question. And I think we ought to address the question that has been raised by CMS, which is, is it

appropriate to divide the population, is it possible to divide the population with hopes of identifying within the MADIT II population a group of people who, in whom the effect of ICD is in doubt or so small that we wouldn't use it. I think we need to address that because CMS has raised the issue in their analysis and we have to really help them with that. Yes, Dr. Curtis.

Dr. Curtis: If I could start it off, you know, I think a comment that was made this morning was so important to this deliberation, the fact that this trial is a well designed randomized clinical trial and it has a positive outcome. And I mean, you might be concerned about issues like cost and all that sort of thing, which is not what we're deliberating today, but that to me is where the impetus starts coming for trying to subdivide everything and see if you can find some group.

I mean, it would be nice if we had risk stratifiers that could tell us that some patients wouldn't benefit, but this trial didn't do that. This trial was designed to be simple, to apply in clinical practice, where you could take patients that had low ejection factors, they had a prior MI, you put a defibrillator in and there was more survival than in the ones who don't get it, and that's the bottom line. You can't take that trial and then start picking out EP study results and do anything with it.

And the comment I wanted to second is the fact that if the trial were negative and somebody came in here and said well, I know the trial's negative but if I subdivide it like this, this group works, we would throw them out of the room, okay? We know that. You know that wouldn't get through the FDA or anything here. So here we have a positive trial result and then to take that and turn it around and say well, but I don't like the idea of applying it to everybody so I'm going to start trying to subanalyze things, the trial wasn't done that way, the conclusions that you're going to draw about EP studies out of MADIT II would be invalid because they are post hoc subgroup analyses. They may generate hypotheses, maybe it would be good in the future to look at a study like that, but this study was not designed that way and it's not going to give you that kind of answer.

Dr. Sox: Let's talk about that. Basically, is it legitimate sort of at a policy level as well as at a statistical or scientific level to raise the question about subgroup analysis? I think that's a great question and I think CMS, we need to hear what CMS has to say and we need to reply, if only in our vote. So Steve, could you address the question about the sort of subgroup analysis that we're doing? It's not the sort of thing that ordinarily would get very far at a manuscript conference at a journal.

Dr. Goodman: No, I would agree with what you said almost to the word. Except, I think one of the important issues here is to distinguish a hypothesis and a subgroup analysis that came from this trial, as opposed to a subgroup analysis that in fact was generated by prior trials. You see, the

hypotheses here are being explored not because they were suggested within this trial. In fact, there has been quite vigorous debate about whether we even have the information to address that subgroup issue.

The issue is that these hypotheses have been raised by prior research and prior knowledge, so this is the not the same of subgroup hypothesis generating issue that we normally confront, which is that we do a trial, we have indications, and then we try to dice and slice it, and claim legitimacy for some subgroup on the basis of that slicing. In a sense, and you can debate this, this slicing was already suggested buy either prior trials -- again, this can be debated, this is free to discuss, or what is known about cardiac electrophysiology.

So it doesn't quite have the same status as the kind of subgroup analyses that I think you very rightly criticize. It did not arise from this trial, it arose from trials with more restricted entry criteria which suggested this hypothesis in the

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first place.

Dr. Wilkoff: Which trial are you talking about?

Dr. Goodman: I think the trials that use the EP testing as the -- like the MADIT I trial, but I'm saying this is for you to discuss, whether the issue of inducibility that was used, whether inducibility which was used as an eligibility criteria for the other trials, which showed efficacy, is a legitimate thing to explore in this trial. It's not the same as a subgroup hypothesis that's generated within a particular trial, it doesn't have the same status.

I think some of these issues are legitimate that are being raised, but to say it's automatically impugned because it's a subgroup of this trial is not I think, I don't think that completely stands. I think it's a subject of debate, how legitimate this hypothesis is, and that's one of the questions on the floor.

Dr. Curtis: But I would say if I was going to look at anything like this, and I know it's data that you said you didn't have, but to know that there were EP negative patients before the trial who got randomized and look at those outcomes makes more

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sense to me than the analysis you were showing where, you know, making assumptions about how many people would or would not have been inducible, and type of patients.

Dr. Goodman: I would have been delighted not to have had to make those assumptions. If I had had that data, I certainly would have tried to use it as best as I could.

Dr. Sox: So Steve is basically, I think, asking our advice as expert electrophysiologists about whether it's reasonable on the basis of prior studies and what we know about the biology to ask the subgroup analysis questions. And I would really like to have, if I can, each one of the experts address that question. Jonathan, do you want to --

Dr. Weil: Before we do that, I was wondering if we could perhaps hone that question in a little bit more by focusing on with respect to EP studies, the following question: For patients with less than 30 percent EF, is inducibility a very

strong, or a strong predictor of sudden cardiac death? What is the evidence for that? Because I think that begins to inform the question, and I think we have to look at what studies exist in the very low EF less than 30 percent and the predictability of

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SCD. That would form the strongest evidence to say yes, this is a legitimate hypothesis or question.

Dr. Sox: So, who would like to start? Dr. Wilkoff.

Dr. Wilkoff: Yeah, I will say something. I actually would state it the other way, is non-inducibility a predictor of doing well? And actually, we were talking about these other studies. The only other study that really looked at non-inducibility was the MUSTT trial, which I want to hear Dr. Buxton talk about in just a second. But I mean, there wasn't a difference. This is not EP data, we don't get any EP data out of this trial. We use it as an inclusion criteria for MADIT I, it was an inclusion criteria for the randomized patients in the MUSTT trial.

If we're going to look at EP negative patients, and we're going to get any data from any of these trials, it would have to be in the non-randomized portion of the MUSTT trial. And we have already said that in that group of patients they were at high risk of dying, at significant risk of sudden cardiac death. And so, I don't see that those questions were raised from the trials. We didn't have any data that really said that non-inducible

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patients, from any of these trials, that non-inducible patients were not at risk.

As a matter of fact, this trial is the first time we have randomized data that since you know about two-thirds of them would have been non-inducible, this is the first time we have data that says that a group likely not to be inducible is not only at risk, but also improves the risk when they're treated with an implantable defibrillator. And we can look at lots of groups that are at risk. The difference about these defibrillator trials is now we have a treatment that takes that high risk group of patients and improves their risk. That's the remarkable thing that happened with MADIT, with MUSTT.

And now with MADIT II, we know we have a high risk group of patients, we know what group, know what treatment improves that risk. What we don't have is a strict non-inducible group with randomized therapy. We don't have any data there, and this doesn't produce that either, except by implication because we know about two-thirds of them would have been non-inducible.

Dr. Sox: Dr. Buxton, you ran the major trial which people are referring to, so can we hear

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from you?

Dr. Buxton: I would refer the committee to the handout that Dr. Lindsay gave you in the NASPE presentation, which shows the survival curves from the MUSTT trial relating to ejection fractions less than, greater than 30, and inducibility status. And as we said this morning, inducibility and ejection fraction are both independent predictors of mortality and arrhythmic death or cardiac arrest. The fact is

that the analysis in this trial showed that for total mortality, the patients with ejection fraction less than 30 percent who did not have inducible VT, had a higher mortality risk but the same risk of arrhythmic death as the patients who had inducible tachycardia but better preserved left ventricular function.

The trial did not test and we don't have the data to know whether or not defibrillators reduced mortality in the non-inducible patients. It wasn't part of the trial design. One would assume they would, but that has not been tested.

Dr. Sox: So, I think I heard you say that in the low ejection fraction patients, the death rate was the same in the inducible and non-inducible patient.

Dr. Buxton: Total mortality was higher if

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they were inducible than if they were not inducible to ventricular tachycardia. The total mortality, though, was actually higher for the patients with the ejection fraction less than 30 who did not have inducible tachycardia than the patients with better preserved left ventricular function and inducible tachycardia.

Dr. Sox: Dr. Curtis.

Dr. Curtis: I think many of us who are electrophysiologists would put this information together and say that for patients whose ejection fractions are between 30 and 40 percent, there is some value to the EP testing in terms of risk stratification, but when you get below 30 percent, that the risk of dying starts to go up so high that it's not reassuring enough, or you cannot be comfortable that the patient will survive if the EP study is negative.

And so looking at that, I would tend to think that as the ejection fraction drops below 30 percent, the patients still are high risk, not trying to risk stratify them, because the EP negative patients still have a high mortality rate. Those patients should be getting defibrillators, but still using an EP study as a risk stratifier for the

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slightly higher ejection fractions, from the clinical trial data we have, still makes sense.

Dr. Sox: I would like to hear from other cardiac electrophysiologists about Dr. Curtis's statement. Do you agree with it?

Dr. Carlson: I wanted to thank Dr. Buxton earlier for answering the question that I thought was the key question, and he answered it again very well. In the patients with reduced ejection fractions, the absence of an inducible arrhythmia is not sufficient to give us comfort and not to implant a defibrillator. So I think that if the first question is, is it appropriate to do a subgroup analysis here, and Dr. Curtis believes that it is not. But if you do a subgroup analysis, then I think the most important question is the one that Dr. Buxton addressed and that Dr. Lindsay addressed in his presentation, and it suggests that in this group that is at higher risk because of their markedly depressed ejection fraction, that the EP study doesn't give us the comfort that we need.

Dr. Sox: Dr. Redberg.

Dr. Redberg: I think what we're really trying to do is define the group that's going to most

benefit from AICDs because clearly there is a group
that benefits, the MADIT I criteria, but you know, how much benefit is there? Because if you make the analogy that like valve replacement, you know, we know replacing the valve for someone with severe regurgitation is going to benefit them. But on the other hand, you don't do it until someone really needs it, because then you start a whole other series of things.

And what I think, you know, certainly low ejection fraction identifies higher risk, but is that good enough, because if 19 percent of those people had defibrillators go off, you know, the TEC study cites Rosencrist's article from 1998 saying that there is a 50 percent adverse event rate with ICD placement in the first year. Well, that's a 50 percent adverse rate versus a 19 percent for the defibrillators. You know, the articles from Ellenbogan and Jack last year that says there's a 37 percent cumulative probability of leaf failure with ICD placement. And there are, you know, other quality of life issues.

I mean, I certainly have lots of my patients come in who have ICDs and in some it's fantastic and some say to me if they had known what it would be like, they would never have gotten one,

because they're like just miserable. They feel like they got kicked in the chest by a horse every time the thing goes off and they would rather be dead.

So obviously there is a population that benefits, but I think we want to define the population that it benefits as well as we can because this is not, you know, a procedure that doesn't have a downside too. I mean, there are adverse effects, there's death, infection, there's leaf failure and the quality of life issues, and as far as I know, we don't have quality of life data at this time to look at from the MADIT studies.

Dr. Sox: Other comments?

Dr. Bigger: I would say that subgroup analyses are never definitive, but as subgroup analyses go, the one that Dr. Moss showed this morning was rather elegant. It's not definitive, but it suggested that people who are EP negative and known to be so before randomization showed significant benefit from the ICD that was similar to the overall result, in fact almost identical to the overall result. My comfort level went way up when he addressed that in that way.

Dr. Sox: He also pointed out that inducible patients were more likely to trigger the

ICD for ventricular tachycardia but non-inducible patients were more likely to trigger it for VF, which struck me as there was discrimination there, but unfortunately it was in a different direction depending on the type of arrhythmia, and in many respects VF is what we're most concerned about.

One thing I wondered about, this issue of the inducibles being sicker generally, is it possible they are sicker because they are survivors, because they are non-inducible, that they haven't -- all the patients who were inducible basically died, and so the non-inducible patients have more time to accumulate comorbid disease and so forth. Any

thoughts about that?
Dr. Buxton: I don't think you can draw that conclusion. In the MUSTT trial we published an analysis that appeared in circulation in 1996 to see if we could find any kind of clinical predictors that discriminated between patients who had inducible tachycardia and those who didn't, and we could not.
Dr. Sox: And that was also true in MADIT II.
Dr. Carlson: I wanted to ask Dr. Moss, the information that you used to discriminate between how sick these non-inducible patients were as opposed

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to the inducible was from enrollment, right?
Dr. Moss: Yes.
Dr. Carlson: That should answer the question. It was from enrollment, so it wouldn't be due to longer survival.
Dr. Sox: Yes, Dr. Matuszewski.
Dr. Matuszewski: One of the things that struck me about the inclusion criteria for MADIT II and then the results is that the mean ejection fraction for the MADIT II population was about 23, and where -- is there any evidence or is there any anecdotal confidence that 31 in terms of an ejection fraction is not appropriate for an ICD and 30 is? Is there some curve, is this a linear line and 30 is just 50 percent do better or not? Or do we have to go as low as 23 before we really start seeing the true MADIT II type results of survival?
Dr. Moss: The mean EF is 23 percent. The cutoff was 30. God didn't come down and suddenly put a criteria at 30. It's based upon our prior experience with a variety of different trials. There is obviously in the reading of ejection fractions by radionuclide angiogram some variance. We went by the written report, the documented report and we just arbitrarily made that decision at 30. We could have

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made it at 31, we could have made it at 29, but 30 seemed like a reasonable value. I don't think you can differentiate between 31 and 30, but you can certainly differentiate between 30 and 20, and 30 and 25. So we took an arbitrary cut point of 30 based upon the written interpreted formal record for ejection fraction.
So, let's take this as an example of Vice President Cheney. He didn't actually qualify for MADIT I criteria, because his ejection fraction was 40 percent. He received a defibrillator based on MADIT I criteria, but he was a little bit over the edge. Of course now the question is, who paid for it.
(Laughter.)
Dr. Sox: I have a question for you, Dr. Moss. As I understood, you compared non-inducible patients who got ICDs with all of the conventionally treated patients and you showed a 32 percent risk reduction after adjusting for the clinical predictors of death, and that was similar to the risk reduction for the inducible patients. My question was, were the inducible patients also corrected for those same predictors so it in fact was a parallel comparison?

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Dr. Moss: Dr. Hall will answer that.
Dr. Hall: We did similar things to

comparing the ICD inducibles to all the conventionals, adjusting in the same way, and we get a better hazard ratio, we get .47, .68 for the non-inducibles, .47 for the inducibles, but both very good results. There's a suggestion, certainly, that the inducibles do better. There's a suggestion, more than a suggestion, that the non-inducibles do very well.

Those may look a little contradictory but also, we did the same analysis for people who didn't have EP tests, the ICD group without any EP testing versus all of the conventionals, and there the hazard ratio was .89. Those are the folks that weren't getting much effect.

Dr. Sox: Thank you.

Dr. Hall: People who ought to have the EP test just don't do it.

Dr. Sox: Kerry, you haven't had a chance yet. Go ahead.

Dr. Lee: I think we all know there is much that can be said about subgroup analyses in these clinical trials and we don't need to reiterate all of those principles that I think have become

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rather well established. The reality of the situation that we're talking about here though, the MADIT II trial, is that based on the subgroup analyses that the investigators have performed and the additional subgroup analyses that we've heard about today, are all remarkably consistent. Remarkably consistent. There is no statistical evidence of heterogeneity in any of these subgroups.

I think the pretrial EP negative data that we've seen today, where the hazard ratio, the relative risk was .46 in patients that were EP negative based on the pretrial studies, comparing conventionally treated patients versus the ICD treated patients, gives an even more dramatic result. Even the results that we heard from Dr. Goodman, I think we would have to conclude were reasonably consistent with the overall results of the trial. That is, no evidence, no strong evidence of any heterogeneity with respect to this matter of inducibility.

So, I think given that remarkable consistency, we can be reasonably comfortable that these results apply very broadly across the group of patients that meet the enrollment criteria for the MADIT II trial. Indeed, one question I think would

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be good for the panel to consider is whether if you had the opportunity to participate in another clinical trial in patients with an EF less than 30 who were not inducible, would you feel comfortable randomizing those patients based on what we know now.

Dr. Sox: Dr. Wilkoff.

Dr. Wilkoff: I would like to address what was talked about, sort of the risk benefit ratio that was a while ago. Only rarely do we actually correct for event rates per unit time. Dr. Moss did it a little bit earlier with the 19 percent versus the 40 percent. The same thing happens with complications. But we also have to talk about the magnitude of what the risk benefit ratio is, and also, we should be putting this in context of how large is this benefit compared to other kinds of therapies that we use all the time. This is a large difference.

I don't know what other cardiovascular therapy has this percentage of difference over this period of time. The shock rate, the anti-tachycardia pacing rate, the therapy rate has always been a statistical thing that has risen over time. Complication rates will go up, but these are not fatal complications, and shocks don't happen time one.

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But let me point out that although you don't get a benefit for terminating the arrhythmia if you don't get a shock, you get the peace of mind of knowing you're protected. The patients today that get their defibrillator put in, it has a profound effect on that patient, it has profound effect upon that patient's family and such like that in terms of the way they live their lives. And so although not all of the benefits -- I mean we're talking about mortality benefit and I think that is convincing to me and I would have a hard time dividing this up.

But I also have to say that there are other benefits that -- and they don't happen all the time -- there are other morbidities that go along with this, bus the other benefits, particularly the reassurance that these patients get during this period of time.

This is a high risk group of patients. The question is, how do we approach these patients in the future? And this is not a small benefit, this is a large percentage benefit that we see.

Dr. Sox: I would like to here from the members of the voting panel. We have been getting some valuable advice from our expert guests, but I would like to hear what you're thinking about,

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especially what questions you have that will help you decide how to vote. Tom.

Dr. Holohan: I'm going to make a statement that anybody on the panel can disagree with. It seems to me that getting into the weeds about inducibility versus non-inducibility what we're really trying to do is to say this therapy is more beneficial in one subset of patients than in another. Is that a fair thrust of the debate so far?

If that's the case, let me use a non-cardiology analogy. We routinely use radiation therapy in many forms of malignant disease and it's certainly conceivable that in a different stage of a given disease that therapy is more likely to be beneficial in some patients than in others, but we don't routinely apply those kinds of criteria. We apply radiation therapy to patients with, for example, Stage II and III Hodgkin's disease, and don't pay a lot of attention to specific cellular types of Hodgkin's disease which may affect to a greater or lesser extent the benefits of the therapy.

And I guess I have some concerns about the study per se, some that Dr. Hlatky raised and Dr. Lynn raised, but it appears to me that what we're really approaching, circling around so to speak in

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looking at subdivisions of inducibility versus non-inducibility, is trying to stratify this in terms of a relative benefit where it appears that both groups benefit, should you make the cut on a 50 percent benefit versus a 30 percent benefit versus a 670 percent benefit.

Dr. Sox: Right. And the reason we're doing it is that CMS has done an analysis to try to identify subgroups that might benefit less and we're trying to basically advise them as to whether that's getting them anywhere in terms of a decision that has a strong scientific footing. And I guess I'm hearing you say you're hearing that it's pretty futile to try to do that.

Dr. Holohan: I think we could probably be here tomorrow afternoon.

Dr. Sox: No chance.

Dr. Holohan: You know, the 25 percent ejection fraction versus 29, versus 30, versus 31.

Dr. Sox: Great. Sean?

Dr. Tunis: I wonder if Dr. Gregoratos is still here, and Dr. Hlatky, I was wondering if we could spend a little bit of time just probing a bit more into the ACC guidelines and some of the issues that were raised there. Is that permissible to do, Hal?

Dr. Sox: Of course.

Dr. Tunis: Okay. I just have a couple questions for these folks and I think other people may actually have some questions for them as well. But I guess starting with Dr. Gregoratos, it would just be interesting to --

Dr. Sox: Sean, before we get -- that's kind of a change in direction, so if we could, I'd like to make sure that anybody else on the panel wants to follow up to what Tom has said and see whether we're coming to some agreement about that and if not, where the holes are. Others that want to respond to Tom's statement, does it speak to what you're thinking as well?

Dr. Curtis: I think I'm agreeing with him if I say that I don't think we did see anything that is comforting enough that you can, you know, that we have a test or some way of looking at it, that we could not implant defibrillators in a group of patents, and that's okay, and that the survival would be much better in the other group. There is enough risk all across the board here that the EP study as a risk stratifier in this patient population, EF under 30, simply isn't good enough to exclude those patients from implantation.

Dr. Holohan: And if even if it were, what would the proportional benefit be, and I don't think we know that.

Dr. Sox: Thanks for waiting, Sean. I just wanted to make sure we had a chance to follow through on that question.

Dr. Tunis: So I guess the question that -- you know, both of you gentlemen were on the ACC guideline panel. Dr. Gregoratos, you've chaired that panel, and the two-way recommendation reflects some difference of view within the panel or difference of view about the evidence, and I just wondered if you wanted to talk a little bit more about where the panel's main reservations were and maybe a little bit about how the panel when they discussed whether IIa versus IIb where the evidence was against, how those conversations went, and just give us a little more flavor of some of the discussions that led to landing on the IIa recommendation. And then maybe Dr. Hlatky would have some comments about some of the panel's

discussions as well.
Dr. Gregoratos: The discussion was long, as you might imagine. The committee started thinking that this was a IIb recommendation, but the concerns

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were those that I listed up on the slide that I mentioned before. But after a period of mature thought and input from others, we basically felt that the predominant evidence was in favor of a higher level recommendation as a IIa.

The concerns that we had to begin with at that time, again, I emphasize back in June of 2002 when this was finalized, were the same ones that have been discussed here today. Are there subgroups or were there subgroups that could benefit more or less from additional risk stratification, could benefit more or less from an ICD. And basically we concluded that there was no evidence to go that way.

We were concerned about whether patients with a prolonged QRS derived better benefit, higher benefit than those from a normal QRS or less long QRS. And again as Dr. Moss said, there was no statistical -- even though there was a time, there was no difference between the overall less or greater benefit depending upon the QRS duration.

The inducibility issue has been discussed ad nauseam today so I will not bring it up again, but it was an original concern and then the committee felt there was not enough evidence to point us in that direction.

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The heart failure, the issue of why there was a higher incidence of heart failure in the MADIT II defibrillator group was a real concern and we think that there may be an answer following the DAVID trial application.

And frankly, we were concerned about the cost efficacy data that were not available to us.

All those things together finally culminated in a IIa recommendation, again emphasizing that in our view, in the group's view, and there was some dissent and some discussion, but the consensus ultimately was that the preponderance of the evidence was in favor of the recommendation for prophylactic ICD implantation.

I think that's the best I can tell you unless you have anything more specific you wanted to address.

Dr. Tunis: So was it the position of the ACC that every patient with an LVEF less than 30 percent and a history of an MI should have an ICD implanted?

Dr. Gregoratos: The position of the ACC is yes. It's a qualified yes, but it's a yes. We are concerned that there may be inappropriate ICD implantations, and that's why we put down that we

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recommend strict adherence to the inclusion and exclusion criteria. We think that there may be a need for additional investigation to better stratify this whole group of patients, although we don't know that.

And we did recommend for the same reasons as number two above, that the registry be maintained sort of as a post-market surveillance type of problem, a situation that the FDA recommends, that we do have a registry of patients who get ICDs for

MADIT II type criteria to see where it all leads to.
Dr. Tunis: I wonder Dr. Hlatky, if you wanted to comment on any of that. And also, in your written testimony you talked about the selection criteria, sort of a preselection criteria for patients in the trial and I just wondered if you wanted to talk a little bit about that and how that might be factored into the ACC position as well.
Dr. Hlatky: Well, let me say that I was on the committee, but I will speak for myself rather than the ACC, because Dr. Gregoratos is here as the ACC representative and chair of the committee.
I think it's fair to say that there was considerable, the Ia, difference between a I and a II is that there is some division of opinion within the

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community and the question was whether there was complete consensus on this, and I don't think there was entirely within our committee, that it was a blanket recommendation to go ahead with this. And I think some of the concerns that were raised were some of the ones that I raised about exactly who the patients are and which groups it applies to are big considerations.
And I would say the second thing about this is, the question of how generalizable it is, the investigators were very careful, I think, to have a very explicit set of inclusion and exclusion criteria that covered a lot. And what we're seeing today is the quest that a lot of those be shed and we just get down to EF less than 30 and pass them on, and that was not exactly the inclusion criteria for the trial.
So I think the question there is, you know, exactly how far do you generalize it? Do you say, you know, lots of people who are in the Medicare population are not eligible for META II, but they do have an EF of less than 30.
Dr. Sox: Yes, Dr. Weil?
Dr. Weil: I would just, when we look at inclusion and exclusion criteria for MADIT II and for the potential to answer these questions, we should

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also remember, and I would say ask Dr. Moss, could not the same questions be raised about the inclusion and exclusion criteria for MADIT I from us, or the studies for which there have been coverage determinations. And in discussing this, I would just, I'm just concerned that we're focusing on these particular types of tough issues only for one study as compared to many others that have been used already for coverage determinations.
Dr. Sox: Dr. Wilkoff, or who wants to go?
Dr. Buxton: Well, I'll make a comment. Many of the studies in the past utilized, say, post-infarction patients who came through the coronary care unit, so you had a nice log, you could log everybody who came through the coronary care unit and you knew who was excluded, why they were excluded, and you had these criteria, okay? When you get out into taking patients from the general environment where you have many different sources of patients, many different practices, many different laboratories, echo, nuclear, angiography, et cetera, it's a very different type of investigation than starting with only patients who come through the coronary care unit.
So it's very very difficult of how you get

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this, what's the background from which you draw the patients. And what you hope is with taking a large enough swipe of the population, 1,200 patients, is that they are going to be reasonably representative, because you're not preselecting on any given criteria. This is part of the reason we use a rather open eligibility, to get as representative a sample of patients as possible.

We also wanted to include a full age spectrum. We did not have an 80-year old cutoff. We took all patients of any age, 85, et cetera. And I remember the argument, because I have taken care of a lot of patients who had aortic valve replacement at age 85 and did well, and I saw no reason to exclude these patients in this trial so long as they met the entry criteria, et cetera.

Dr. Sox: Maybe I could ask you, we will get into discussion of entry criteria and generalizability after we vote on this first question, and we will have a question for you at that point. Yes, Colleen.

Dr. Conway-Welch: I would just like to clarify one point, and I don't think it's relevant whether the vote is yes or no or whether we do it as exclusion or inclusion. But, am I correct in that we

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don't have any enough data on women to be able to say much of anything about what their clinical sequelae would be. I guess, Dr. Moss?

Dr. Moss: Well, it's a small subgroup. That is the fact, that is was 16 percent of the total population. They did seem to do better by meaning hazard ratio, lower hazard ratio. But being a smaller subgroup or a smaller group, their confidence interval, there is more potential for variability. So we, just like Dr. Buxton mentioned, this is a reality of life and we thought we would get more women by having unrestricted age. We didn't get as many as we would like.

This was also true of NIH supported studies where they by law have to have 50 percent women. They have never achieved that. It's a very tough area and as I said, this is where I think some of the future direction should be, to focus this more.

Dr. Conway-Welch: I understand the problems, I'm just asking for a yes or no. We really can't, I mean they really aren't part of the equation.

Dr. Moss: You can't exclude the subgroup, you can't say it's not effective in women; if

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anything, it looked a little more.

Dr. Sox: Dr. Gregoratos asked if he could make one more statement about consensus.

Dr. Gregoratos: Since the issue of consensus came up, I wanted to tell the panel the final vote. There were 11 members of the committee. One person, an electrophysiologist held out for a IIb recommendation. There was another electrophysiologist who held out for a Class I recommendation. And there were 9 of the 11 who voted for a IIa.

Dr. Sox: I'm wondering if we're getting pretty close to taking a vote on the first question. Would you put it back up please. I guess I would

like to ask the voting panel whether they're ready to vote or whether there are more questions they would like to ask about the first voting question.

Dr. Weil: You're only proposing to vote on the first bullet?

Dr. Sox: Only the first one now, and then we would move on to the second one.

Dr. Tunis: I just want to make sure people understand the distinction between the questions which I think you were trying to get at which is, and people can correct me if I'm wrong, but

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I believe the first question is basically, is the evidence adequate to draw conclusions about health outcomes in patients identical to the patients enrolled in the MADIT II trial? And the second question would be, is the evidence adequate to draw conclusions about patients, all Medicare patients with LVEF less than 30 percent who are post-MI, which gets to the issue of generalizability?

So does that seem -- if we sort of rephrase the question that way as question number one is that stuff, but for Medicare age patients identical to, or for patients identical to the patients enrolled in the MADIT II two trial, and the second question would be all patients with left ventricular ejection fraction less than 30 percent and post-MI.

Dr. Sox: So you're proposing to insert something that would say Medicare age patients identical to those who met the MADIT II criteria?

Dr. Tunis: Or identical to the patients enrolled in the MADIT II trial.

Dr. Sox: It doesn't sound like a particularly substantial difference to me, as long as the panel is comfortable with it. Tom?

Dr. Holohan: I would argue the other way

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around.

Dr. Sox: Please do.

Dr. Holohan: A group of patients who met the inclusion and exclusion criteria for the MADIT trial is different than saying patients in the MADIT trial who are identical to other Medicare patients who are beneficiaries.

Dr. Tunis: Right. I guess what I'm also trying to get at is it's not just the inclusion and exclusion but also trying to incorporate this notion of the selective referral for consideration of inclusion in the trial, given that what appears to be a somewhat sicker than average population based on two and three more mortality in the conventional study arm, but if you wanted to leave it as inclusion and exclusion --

Dr. Holohan: Well, I think that's what, if you want to be that specific, I think you have to be that specific.

Dr. Weil: I would just raise the issue, is that how similar questions have been posed with, in previous panels, with respect to clinical trials?

Dr. Sox: In general I don't think we have had the luxury of having many clinical trials, and perhaps this one being so complex, I don't think we

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have actually divided a question before, so I don't think -- the answer to your question is, I don't think there's a precedent.

Dr. Weil: I would just be concerned that to attempt to narrow down really a gold standard for evidence based medicine in that way, as compared to other types of evidence that the committee panels have considered before, that I believe it may be a counterproductive precedent.

Dr. Holohan: So are you then saying eliminate the inclusion and exclusion criteria?

Dr. Tunis: I leave that up to you.

Dr. Weil: No, I would propose leaving the question as it is, but to add terms like identity, et cetera, would appear to make the question extremely limited and not necessarily as useful to the types of coverage determinations that CMS will have to make.

Dr. Sox: Well, CMS is going to -- we're just advising them and we may be slicing this a little fine for their purposes, since what we say isn't necessarily going to be translated directly into coverage rules. Dr. Curtis?

Dr. Curtis: Every clinical trial has inclusion and exclusion criteria and can be as

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narrowly defined as you want or as broadly defined as you want. And then when the trial is published, the results tend to be used in a more generalized way than whatever the trial was. And there are degrees to which that happens. I think in the MADIT II trial the fact that the inclusion criteria were really rather simple overall, the fact that it was a low ejection fraction and ischemic cardiomyopathy tends to make this more generalizable than other trials that you might consider. And so you know, and I guess as a corollary to that, Medicare coverage or CMS coverage of this indication, what we're talking about is allowing reimbursement for coverage for this indication, not mandating it.

I think what we have to realize is that physicians who take care of patients, hopefully most of us are not going to forget things like somebody with an otherwise terminal illness or other reasons, you use good clinical judgment. You don't implant defibrillators in patients with dementia who are in nursing homes just because they meet the MADIT II criteria. We do use judgment there. But I think aside from that, with good clinical judgment, this is a fairly well generalizable trial.

Dr. Tunis: That's the whole point, that

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we are trying to give the panel the opportunity to vote on the extent of the generalizability of the trial by having two separate questions, one that deals with internal validity and one that deals with generalizability, to see if the panel agrees with your point of view.

Dr. Conway-Welch: I agree.

Dr. Redberg: The question was raised by Dr. Hlatky, based on what you said, that only 3.8 patients per year were enrolled at each center, and that's what led to the idea if it was so generalizable, why was enrollment so low and were there other risk markers, or what was going on with enrollment that there were so few patients and so few women, and I don't know if we have any minority data from this trial.

Dr. Moss: Well, any time you do a new clinical trial, it's a challenge to enroll patients.

That's why we went to 76 centers. Now if you take the -- any very large trial to get large numbers, you need a lot of centers and that generally means that the enrollment rate per center is somewhat low. This is true I think if we were to ask Dr. Buxton to get his 800 or so patients over five years, and it's a challenge. It's even more of a challenge now with

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human investigation; we had to get human investigation committee approval in every center, and it's a challenge. I don't know how else to answer that. I don't know any center that can enroll a large number of patients very very rapidly when you're doing an intervention trial of this magnitude.

Dr. Sox: So it makes it fairly tough, doesn't it, to generalize from the study population to almost anything else? And maybe that's one reason for trying to frame the question in a way that I think is relatively narrow, because at least we can try to answer that question because we have the study before us, and we have now discussed it pretty thoroughly in terms of trying to decide whether we can slice and dice the population, and decided I think probably that we can't.

So, other questions? Otherwise, I would like to move on to a vote on the first question. Let's go for it. So, I will now turn you over to Janet.

Ms. Anderson: One thing I have to do for the record.

For today's panel meeting, voting members present are Tom Holohan, Colleen Conway-Welch, Anne Curtis, Carole Flamm, Alex Krist, Karl Matuszewski,

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Rita Redberg. Chairperson Hal Sox will vote in the event of a tie. A quorum is present. No one has been recused because of conflicts of interest and at this time the chairperson Dr. Hal Sox will call for a motion and ask the voting members to vote. It will be a yes or no vote.

Dr. Sox: Would somebody like to move the question?

Dr. Curtis: So moved.

Dr. Sox: Do I hear a second?

Dr. Flamm: Second.

Ms. Anderson: So we're voting on the question as listed in bullet point number one. Those voting members who are voting yes, please raise your hands.

(Show of hands.)

Ms. Anderson: Those voting members who are voting no, I have to say even though it was obvious.

(No response.)

Ms. Anderson: We have a unanimous vote for yes, thank you.

Dr. Sox: So now we need to move on to the second question, which is effectively the generalizability question. Is the evidence adequate

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to apply the findings of the MADIT II trial to all Medicare patients who meet the inclusion criteria for the MADIT II trial?

And I guess one question I've got is whether we want to state it just that way or whether we might want to say all patients who had a myocardial infarction and who have an ejection

fraction less than 30. Should we sharpen it a little bit by making it more specific?

Dr. Holohan: That's very different, because the inclusion and exclusion criteria are a smaller population than people who simply have had an acute MI and an EF of 30 percent.

The other question is that in the first bullet we talked about inclusion and exclusion, but the word exclusion doesn't appear in the second bullet.

Dr. Sox: Well, I think that's to ask th question basically of whether we know enough right now to predict the results of applying the MADIT II trial to all patients, including patients who have illnesses that are likely to prove fatal in the near term and the like. That's the question we need to talk about.

Dr. Wilkoff: Why would you ask the

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question whether it was effective if you want to generalize it to patients who were going to die from something else? I mean, who would argue that you want to implant these devices in people who are going to die from other causes?

Dr. Sox: I guess we want to advise Medicare on whether to encourage that sort of thing by covering it.

Dr. Wilkoff: Well, I would propose that you, that particular exclusion criteria belongs there. The point is, that's what physicians do. I mean, physicians don't apply any therapy to people that have other life limiting problems. I mean, that's part of the practice of medicine, but it's not going to inhibit anybody if you say you can't put it in, that Medicare shouldn't be covering patients that are going to have a near-term mortal illness, that's not going to inhibit anybody's practice. I don't think we have to argue about the generalizability to that group, do we?

Dr. Curtis: I totally agree with Bruce. It goes back to what I said about mandating implantation versus allowing implantation. I mean, I don't think anybody here would recommend operating on an aneurism in somebody with terminal cancer either,

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even though that's reimbursable or allowable. You have to use good clinical judgment, but I don't think that the voting question ought to be if somebody has major other comorbid illnesses, whether or not this is generalizable. I think the understanding most people have is that if somebody has serious other medical illnesses, that good clinical judgment would lead you not to do that. What we should be voting on is whether or not these results are generalizable to the average Medicare population.

Dr. Sox: Well, specifically the question which Medicare wants to ask is, is the evidence adequate to extrapolate these findings really either to the population that includes the people with near-term fatal illness or other people that didn't meet the trial inclusion criteria.

Dr. Tunis: The nature of the coverage request was as broad as any Medicare patient with left ventricular ejection fraction less than 30 percent and post-MI, that's how broad the request is. So we need this committee, if possible, to vote on whether or not the evidence is adequate to generalize

that broadly based on the MADIT II study. That's the question that we need answered.

Dr. Curtis: Would you be looking for

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explicit exclusion criteria then?

Dr. Tunis: No, we would be looking to get the judgment of this panel about whether the evidence that you have in hand supports as broad a conclusion as yes, this is adequate to basically cover, to basically generalize to all patients that meet those two criteria.

Dr. Sox: Because that's the way that the requestor framed it; is that correct? Tom?

Dr. Holohan: I'm having some cognitive dissonance here. We just voted yes, that the evidence was adequate to draw conclusions about outcomes in Medicare aged patients who met the inclusion and exclusion criteria, we said yes. That's the way we wrote the question, that's what we voted on. Now we're talking about expanding that, throwing out the inclusion and exclusion criteria and saying anybody who is a Medicare beneficiary who meets only two criteria, not the inclusion and exclusion criteria for the evidence we have been listening to all morning. I find it a step that I can't take based on the evidence.

Dr. Sox: Then you would vote no.

Dr. Holohan: No. What I'm saying, or what I thought I was saying is I think the question

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doesn't make a lot of sense to me based on our vote on the first one. The question itself doesn't. If that means vote no, okay.

Dr. Tunis: Part of the question, Tom, it's a question of how far beyond the long list of exclusion criteria and inclusion criteria specifically in the MADIT II study would this committee be comfortable thinking that that evidence allows for generalization. That's the question, so we're trying to frame it, you can frame a different question, but the point is all you've voted on is yes, the evidence is adequate to cover someone essentially identical or who meets all the inclusion or exclusion for the MADIT II study. What we're trying to get at is how far beyond that does this committee feel the evidence is adequate to go, and does it go so far as to everyone with the two criteria, post-MI LVEF, which is what has been proposed as a coverage decision.

Dr. Holohan: I will defer to the experts on the panel. I just don't see a long list of inclusion and exclusion criteria in the New England Journal paper. They're fairly limited.

Dr. Curtis: You know, if we could amend this to -- I mean, maybe the sponsor came forward and

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said, you know, EF under 30 and they've had an MI any time, I want this covered. There really are a limited number of other criteria here that I don't think most of us would probably have a problem with, you know, an MI within a month, the revascularization within three months, that was in the exclusion criteria. Wasn't that CABG? And what about Class IV? Yeah, Class IV heart failure. I mean, you can make a very minor adjustment to that that I think most people would accept, and then we would be happy with.

I'm very concerned about being locked into, or asked to vote on a question that by the way you're phrasing it is going to demand a no answer, and it's not going to get at what we're really trying to do, I don't think.

Dr. Redberg: I wonder, because I think there are questions that are going to be impossible to generalize, not only all the inducibility things that we talked about but just, I mean the big question. Women are more than half of the Medicare population and 15 percent of this trial was women. The hazard ratio crosses 1, well into 1.2, and I'm just wondering, I think we need more data about women, besides some other categories of the general

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Medicare patient.

In the past occasionally there has been a conditional coverage because often data isn't collected once the coverage determination is made, not at least for clinical trials, and would there be a possibility to continue, for Medicare to have sort of a conditional coverage in the context of continued randomization clinical trial format where we could answer some of these questions that we're not able to answer from the MADIT II data, like in women, minorities and other groups that people are questioning?

Dr. Sox: Sean, would you address that question, the concept of some sort of provisional coverage for people in trials who don't meet the criteria we just voted on?

Dr. Tunis: There has been a limited number of cases where we have done something like that and so while it's not impossible, it's not a common thing for the Medicare program to take on.

Dr. Holohan: What about the registry suggested by the ACC?

Dr. Sox: Well, there are a number of things that we could suggest as part of our recommendation, and I think the ACC recommended

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strict adherence to the MADIT inclusion and exclusion criteria, a registry, and at least one other thing.

Dr. Curtis: Actually, I think one other thing that should be brought up is that there is, we're implanting a large number of resynchronization devices today, biventricular pacers, and they are for heart failure patients. And we can't get into a long discussion now, but there is a relevant point here. Today if you have a patient with Class III or Class IV heart failure, we can implant the biventricular pacemaker because that's a covered indication. But when we get these patients with ejection fractions of 20 percent and they're Class III and all the rest of that, and we're putting hardware in anyway, with this kind of trial results, I think most of us as electrophysiologists would really prefer if we could, to implant the biventricular defibrillator in somebody with an ischemic cardiomyopathy with a very low ejection fraction, and I think there is evidence there to cover those patients, and I would hate to say that be excluded.

Dr. Wilkoff: And particularly the functional Class IV patients, which would be excluded if we strictly adopted this, would be excluded from that. So my opinion would be, if we're going to

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generalize this beyond this strict criteria that we have here, we should generalize it to the functional Class IV patients, because if anything, we have evidence that it may benefit more of those patients, and we do have the provisional data from Companion, which also is in concert with that. We may not have hard data there, but if we're going to talk about generalizing this data beyond the strict criteria, functional Class IV patients I think should not be excluded from this indication.

But I think waiting a period of time, a month after MI, three months after coronary intervention of some sort, is not an unreasonable thing, that's certainly the population that we had here, and there's no reason to have to generalize beyond that. That's the way I look at it.

Dr. Sox: Well, we're not quite at an impasse here but we're not exactly on the same page, I think. We're supposed to comment on the adequacy of evidence, that's our job. And the question that we're trying to get at and we still haven't figured out how to get at it, is how good is the evidence that the MADIT II criteria apply to patients beyond those that were in that trial? And that's what I think CMS wants us to comment on.

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And Dr. Wilkoff suggested that maybe there is some evidence that in a particular subgroup of patients, namely Class IV heart failure, that there is enough evidence that we could generalize to that group, and maybe there are some other groups where there is enough evidence to generalize to that group, and if so, we ought to discuss that evidence and see if we agree that it's good enough to generalize. But the intent here is to ask, is the evidence good enough to generalize to patients who've had an MI very recently, revascularization very recently, or patients who have another condition that's likely to claim their life in the short term, how good is the evidence that the study applies to those patients? Now, are we coming to any understanding of this?

Dr. Curtis: All right. Maybe this will help me understand it and other people here too. Let's say we said no to that, then what? Where do you go from there?

Dr. Sox: Well, he's the one who makes the policy. We just advise him on the evidence.

Dr. Curtis: Then I don't think that's the right question to ask, but if you're saying that is the question you want answered then I want to know what it means.

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Dr. Sox: Well, our job is to try to answer questions useful to CMS, because our job is advising them, so what is a question that's useful to you, Sean?

Dr. Matuszewski: I could offer one throwback to that, and we will wait until more evidence develops. This is amazingly an area where there is not a lack of RCTs, there is not a lack of trials in progress where the results will be due in 2004 and in 2003 where -- I don't think we have to say that this is the one time we're going to deal with it and forever more it will be done. Maybe it's somewhat pessimistic but you know, you'd like to see a little bit more. I can tell Sean the exclusion criteria of women of child bearing age who won't take

contraceptives, that one won't work for you. But the New York Heart Association Class IV, there were nine patients who snuck into MADIT II even though that was an exclusion criteria, so there was some leakage.

With that second bullet there, you know, you'd love to say it looks like something, but wouldn't it be better if we had some more data, but we don't expect any more trials to come down the pike, but I don't think that's the case here.

Dr. Weil: I would ask the question with

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respect to the indications of EF less than 30 and prior MI, are the studies coming down the pike, do they address those particular criteria, the SCD-HEF and any other that is almost complete?

Dr. Buxton: The ongoing trials do not examine the same populations. They examine patients with non-ischemic dilated cardiomyopathies, which is an entirely different physiology. They examine patients with congestive heart failure, and that's a different population with different risks. So this was not a heart failure trial, it included patients who had heart failure but it was not a heart failure trial and it doesn't duplicate, SCD-HEF will not duplicate these results.

I would just add one thing for the people that are concerned about, it seems some people are concerned that the defibrillator doesn't work in women or that there's not the same degree of benefit. We have an analysis that has been prepared but not yet published, only presented as an abstract in MUSTT, that shows that women benefitted from defibrillator therapy to the same degree as men, among patients randomized in that trial.

Dr. Tunis: I'm wondering if I could ask someone from Guidant to clarify, since we can't seem

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to find a copy of the coverage request here in the room, what was the request for coverage to CMS for?

Dr. Smith: I'll get up in the absence of that information. I think somebody is going to give me that in a minute, but it seems like you're struggling with trying to answer the question if our request exceeds the bounds of the trial. We're going to stick to the science. And so, a coverage indication that speaks to the trial I think is what we're asking for. We're not asking for more than that, we're sticking right to the science.

So if it's written in a way, if the request is written in a way that makes it look like we're asking for more than that, that's not the case. What we want to get is what the trial allows us to ask for with respect to the science. So, to be specific, I think if you're including the inclusion and exclusion criteria in the questions, then that is the trial and that is the topic I think we're asking for in terms of your deliberations.

Dr. Tunis: So, you know, another way to get this committee on record on this issue of generalizability, if we wanted to phrase the question as, is the evidence adequate to apply the findings of MADIT II beyond the inclusion and exclusion criteria

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of MADIT II, maybe you can answer that question with a clear conscience. I know you're reluctant to say no, but --

Dr. Curtis: Yeah, because you know, when

you talk about generalizability, I think what you're asking for is if you have a set of inclusion and exclusion criteria, and how much more do you go beyond that, you know, I don't want to say that anybody with an ischemic cardiomyopathy with an EF below 30, let's go ahead and put defibrillators in everybody, or that's what the evidence says. I mean, I'm glad that you just said that, because the trial has a certain matter of inclusion and exclusion criteria, that's what we have the evidence for, and I think that's what I would like to vote on eventually as a coverage thing. If you're saying, you know, do we think you can generalize beyond that, and by that you mean throwing out the exclusion and inclusion criteria, I don't think we should or would want to do that.

Dr. Sox: It kind of sounds like we all want to do the same thing but we can't figure out procedurally how to do it. Yes, Dr. Weil?

Dr. Weil: This is because as several people have pointed out, we haven't had such good

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RCTs in this panels before we reached this point. I do remind everybody on the panel that they are allowed to consider other evidence in addition to RCTs. We just have such good studies in this case that we've had the luxury of relying primarily on them, but if based on other types of evidence, that can inform their decisions as well.

Dr. Sox: Let me ask the voting members now, would you be comfortable voting on this question? If not, how should we modify it so that you feel you're being able to vote yes or no and be expressing your opinion on the matter, the second bullet.

Dr. Holohan: I would ask that exclusion criteria be included just as it was in the first bullet.

Dr. Sox: But then it's the same question, Tom.

Dr. Curtis: The only think I think that we really should think about is the class, really the inclusion and exclusion criteria, one says MI a month or more before, and the exclusion criteria says if you've had an MI within a month, so they're saying the same thing in different ways, so you don't have to worry about that. So really the biggest

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differences between the inclusion and exclusion criteria, aside from the child bearing age or whatever, really has to do with recent coronary revascularization and the Class IV issue.

The Class IV patients, I would be reluctant to exclude because of the issue of resynchronization devices, because if you have a resynchronization defibrillator, the resynchronization part is supposed to improve the heart failure and then the defibrillator is supposed to prevent sudden cardiac death. If you said that you could implant to the Class III but not a Class IV, that's going to give us an awfully funny group of patients that we can't take care of, and that's probably the ideal treatment for them.

Did this trial cover that? Absolutely not. But that's where I think you get beyond the RCT issue and say, you know, we do see benefits in these patients. And not only that, but the Companion

trial, which was a resynchronization defibrillator, showed an improvement in survival.

Dr. Wilkoff: Perhaps what we should say is functional Class IV patients with a wide QRS, because that's the particular problem group of patients that we would be seeking to be treating. I

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mean, functional Class IV patients that have a high mortality from heart failure that we're not going to resynchronize probably is not a great patient for this, but a functional Class IV patient that we are going to resynchronize, has a wide QRS, would be a good group.

Dr. Sox: Let's try sticking in a parenthesis on this and see how it flies. Start a parenthesis at the end of the sentence. Other than patients, and here's where I need the wording. With Class IV and a wide QRS, what do we put in there.

Dr. Curtis: Class IV with a narrow QRS, or normal QRS, because you wouldn't resynchronize them. Was that inclusion? Yeah, other Class IV --

Dr. Sox: Well, we want to put in the group of people that we think should get the ICD.

Dr. Curtis: All right, I'll take your word for it. It should be a wide QRS?

Dr. Carlson: I think what you're doing there is to exclude the patients with Class IV and what you want to do is add the patients with Class IV.

Dr. Sox: We want to include that group but exclude other people.

Dr. Curtis: So it would be including

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patients with Class IV CHF and a wide QRS, right? Okay.

Dr. Sox: So, I'm confused now, because what I'm thinking is that most of us feel that the evidence is not adequate to apply the MADIT trial findings to all Medicare patients who meet the inclusion criteria for the trial, and I think we all believe that, it sounds like. But now we want to make an exception to that, for a group which we feel it does apply to, so --

Dr. Wilkoff: I think what you want to do is word it like the first question that we passed already, and just add in the parenthetical phrase, which will add in just one other subgroup, just a small generalizability.

Dr. Lee: Add the parenthetical phrase to the first question. I think that's what Dr. Curtis had in mind. You were comfortable with all the exclusion criteria except for those in this parenthetical phrase.

Dr. Curtis: That's correct.

Dr. Sox: So, you want to put the parenthetical phrase in the first question?

Dr. Lee: Make it a second question. Keep the first question the way it is. Add a second

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question that's just like the first one, but add that small subgroup.

Dr. Sox: And then we can vote on that question, and then we can go on to vote on the third question, which is the one we've been talking about the last 20 minutes. Kerry, can you make those changes?

Dr. Moss: Dr. Sox, the comment I was

going to make is I would suggest the committee needs to be very cautious about focusing on this specific subgroup of Class IV patients with a wide QRS. And the reason I say this is that although, you know, the Companion study is obviously a very important trial, the committee does not have the benefit of a peer reviewed publication with that information outlined in sufficient detail to really fully understand the implications of the use of these devices in that group of patients. I just think caution is warranted.

Dr. Holohan: I have to agree. We haven't reviewed evidence to that effect.

Dr. Sox: Well, if we can ever get the question down in a form that we can vote on, then we can have a discussion about it.

So as I understand it, the proposal is

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that we create a new question that basically asks, does the MADIT II trial data apply to this subgroup of patients with Class IV CHF. Is that the idea?

Dr. Curtis: I guess the biggest problem I'm having with the question altogether, maybe phrasing it this way will help, in patients with atrial fibrillation and risk factors, anticoagulation is indicated, okay, and we use it. Now if I had patient with a recent GI bleed, I wouldn't anticoagulate them. Because there are some Medicare patients who have had a history of GI bleeding, do I not then generalize it and say it's indicated in all Medicare patients? No. You use good clinical judgment and you say I have a reason why I can't use it in this patient.

Yet the way the question seems to be phrased, it seems to be that we're being asked to say okay, we're going to just broaden it and use it in everybody, and that's not how we practice medicine, so I feel very uncomfortable with the way this is going.

Dr. Sox: Well, suggest some wording that will express your feelings. Help us.

Dr. Wilkoff: So you don't want to generalize it, you want to use it specifically to

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identify what the criteria or the evidence that we have. Is that right, Anne?

Dr. Curtis: Yeah.

Dr. Wilkoff: Okay. And you're suggesting that if there is going to be a generalizing at all, the generalizing of that additional criteria would be to add patients that have functional Class IV heart failure and wide QRS, to allow us to -- I mean, we could discuss whether we should generalize it at all, and if we are in agreement that if it's strictly defined, that it's okay, so if we want to generalize it just that one little bit, I don't know that we have to argue, or to go any further than that. So you just word it just like the first question, but just add that one little subgroup, and we can talk about it.

Dr. Curtis: I'm okay with the way that says it now.

Dr. Weil: I think there was a little bit of confusion because Dr. Sox was restating the question a little bit differently. He was, and I think this is important to reemphasize, are we deciding or are we voting saying we will only

consider the MADIT II evidence to determine this, or will we consider any evidence brought before the

panel. And I think including clinical experience evidence, et cetera, which may be suitably weighed, and I just want to be clear that that's what we're trying to do here. I don't believe we're actually saying the only thing that may be considered are the specific results of the MADIT II study in applying that second question.

Dr. Curtis: Because several times I think you have read the question and then said some sort of a qualifier, like does it also apply in patients with serious life threatening illnesses, and I think that's where it's coming from, because you're adding that into that question and that's not what it says. So you know, if that's what you want to say and vote on, that's different from the way the question is up there right now.

Dr. Sox: Well, I think the intent is the give the committee a chance to express their opinion about whether there is any evidence that the MADIT II trial data apply to patients other than those in the trial. That's what --

Dr. Weil: Again, I'd just like a clarification. Is this subcommittee solely allowed to consider only MADIT II data and not the broad experience and other sources of evidence that

experienced electrophysiologists are aware of. I think that's what --

Dr. Sox: Well, in a way that's -- I mean, we have a couple of experienced electrophysiologists that throw up their hands at the idea of installing ICDs in patients other than those who met the MADIT II criteria, with this single exception we talked about.

Dr. Tunis: I believe the gentleman from Guidant has some information.

Dr. Smith: I appreciate the clinical dilemma that you might find yourself in, but I think we are all best served by sticking to the data that we've talked about all day, and realizing that indications may expand or contract in time as we learn more, but for today there's one question, and I think it looks just like the first question, only it has that phrase that starts, is the evidence adequate to supply, and then it goes on to say the inclusion and exclusion criteria from MADIT II.

Really, I think that is all we're coming and asking is the data that we're presenting. And I understand the dilemma, and I think we solve that dilemma going forward. But for today, I think the question in front of us is the data that's been

presented.

Dr. Curtis: And I don't want to hurt the whole discussion by insisting on the wide QRS thing. I mean, I really don't have a problem leaving that out if it simplifies the discussion for everybody.

Dr. Sox: Let's take that out, let's vote on that second question, and then we can raise the question about the Class IV patients.

Dr. Tunis: I want to make sure -- we finally have a copy of the tracking sheet with the coverage request from Guidant, which was to expand coverage to include patients with prior MI and an

ejection fraction of less than 30 percent without requiring evidence of arrhythmia. So that was the question I was trying to get you to answer, which is, is the evidence adequate to support those two indications. You may want to abstain on the question, but I'm going to ask the committee to vote on that question, okay, because that's the coverage request.

So the question is, is the evidence adequate to apply the findings of MADIT trial to all Medicare patients with a prior myocardial infarction, ejection fraction less than 30 percent, without requiring evidence of arrhythmia? That's the

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coverage request, and that will be the question.

Dr. Sox: Okay.

Dr. Weil: Can we ask that as a third question? Can we answer the question that was just revised, and then add Sean's question?

Dr. Sox: Well, we have -- let's get this one on the table, let's vote on it and then we can consider other questions, so we make our way to the end of this day.

Dr. Stanton: Dr. Sox, as a second requestor on this, can I make a comment?

Dr. Sox: Sure.

Dr. Stanton: I'm just concerned about the rephrasing of questions at this point in time and the strict reading of the initial request by Guidant, because I think that what is being done is trying to make Guidant's request look like it was broader than it really was. Because I would agree with Joe Smith that when we seconded as a second requestor on this, it is for the MADIT II indication, it was not to try to expand to a broader usage.

Dr. Sox: Thank you. So that's the generalizability question.

Dr. Smith: Sean, do you want the generalizability question? Because I don't think

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we're asking for it. If that's your question, that's fine. We're only asking for coverage based on the exclusion and inclusion in the trial.

Dr. Tunis: I think given the history on this and the amount of discussion, I think we'll leave this question in.

Dr. Sox: So the second bullet is what we're going to vote on.

Dr. Buxton: Can I say something? I don't understand why you want to -- it seems the way you're writing this now, you're not requiring that the ejection fraction be measured at 30 percent or less at least a month after infarction, at least three months after revascularization. Ejection fraction improves in the first several days after infarction. You want to make sure that you have a stable patient, just like the patients that were studied in this trial. The sam thing happens after bypass. So you want to apply the data that you have to your recommendation.

Dr. Sox: I hear you. Now, I'm curious to know how people think they're going to vote on this, because what we're trying to express as a group is the idea that we don't want to extend beyond the terms of the requestor. And so I think that, if I

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were voting, I would want to vote no on that, because

I don't want to generalize it to everybody, I want to keep it within the framework of what the requestor asked and for what I personally believe the evidence covers. I want to just see if everybody understands the question that way, because then we're on the right page, but if we're still having trouble, then we're going to keep working until we get it.

Dr. Weil: I agree with you. I mean, everything we have done today has really focused really on the MADIT II data. If we had been prepared to discuss, and discussed the second question, which does require going beyond MADIT II and for the consideration as someone already mentioned, that would take a great deal of time, so rather than -- I question whether we need to vote prematurely rather than vote on the question below it that we had been discussing, with or without the Class IV QRS. I mean, to vote prematurely on a question that we're not prepared for, I don't think does anyone any good.

Dr. Sox: We're being asked whether the evidence is adequate to apply the findings of the MADIT II trial beyond the MADIT II trial study population, and if you believe that we don't have adequate evidence, you should vote no.

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Dr. Curtis: That was the question I asked before and never got an answer to. Let's say that you vote no there. Are we done, go home, that's it, and you don't cover it? That's my question because that's what it sounds like, because the next question there says if yes. If no, it sounds like that's a discussion closer, if that's a word.

Dr. Tunis: You can go on to question 3 no matter how you vote on question 2.

Dr. Sox: Okay. I'm speaking now just to the people that are going to have to vote. Do you feel like you understand the question? You don't, Carole?

Dr. Flamm: Was our original intent to, we voted on the first piece, and then we were going to vote on the complement of that, sort of the extension of the excluded patients. Is that what we're trying to do here, or are we really trying to vote on the first thing with an extension of without requirement of an arrhythmia? You know, there is just too many kind of rewordings happening here, and I think it's not clear what this second bullet is asking me, because I think there are two parts. It's both extending to the complement of excluded patients and sort of rewording question one in a sort of way.

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Dr. Sox: We've voted on question one and we've agreed that from our point of view, the evidence is such that Medicare ought to cover the MADIT II patients. The intent of question two is to ask how good is the evidence that you can extend it to patients beyond MADIT II patients.

Dr. Flamm: I understand that intent.

Dr. Redberg: If you read the draft questions, it's IIa, it hasn't been changed. It doesn't say without inducible arrhythmia, but that doesn't make a difference.

Dr. Sox: Again, speaking to the people that have to vote, do you think you understand the intent of a yes and a no vote on this question?

Okay. It sounds like I think we understand it well enough so we can take a vote. We

know what the consequences of a yes and a no vote is. A yes vote meant that you can apply it to all Medicare patients. A no vote is it applies only to the patients who were MADIT II eligible.

Dr. Weil: Will there still be a vote on the third bullet?

Dr. Sox: The purpose of the third one is to -- I think the third one will go away and if Dr. Curtis or somebody else wants to add a substitute

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motion that deals with Class IV patients, then we can do that.

Dr. Weil: I mean, the third bullet was without regard to the Class IV patients with wide QRS. It was a slight extension of the first question as well. That was our first generalizable question.

Dr. Sox: If somebody on the panel wants to make a motion about that, we will talk about that. Okay.

Dr. Smith: I'm sorry, I don't want to interrupt, but I read the questions differently perhaps. The first one says is the evidence adequate to draw a conclusion; it doesn't give a direction about that conclusion, it only says is the evidence sufficient to draw a conclusion. It's the third bullet that says is the evidence adequate to apply the findings. And I really think, if I'm judging the sentiment, that is the statement that must be made, not just is the evidence adequate to draw a conclusion, it's actually is the evidence adequate to apply the findings.

So, I'm thinking that the operative thing to trap everyone's impression is the third bullet, right? I think that's what people are voting on, even though it doesn't reflect itself in the text,

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and I just want the text to be reflective of how you feel.

Dr. Sox: Well, I think the second and the third bullets are essentially the same, except in --

The Panel: No, not at all.

Dr. Curtis: I think the first question, is there evidence to draw conclusions, we said yes. Now the next question ought to be, is it adequate to apply the findings to the Medicare patients. You made the second question be, can we generalize it to everybody, and of course you're going to have a no vote, there is no other answer to that one. But if you want to vote on that, that's fine, but I want to make sure there's a third question that we vote on that says, if you apply the MADIT II criteria to Medicare patients, is the evidence adequate to show that you're going to have a good outcome or a positive benefit, and that's the question that should be voted on. That's the important one.

Dr. Tunis: So let's vote on question two and then go on to that.

Dr. Curtis: I think we ought to eliminate question two.

Dr. Sox: Tom?

Dr. Holohan: I just wanted to ask Sean,

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is question two in there causing all this problem simply because of the precise wording in the letter from Guidant to CMS? Is it there in other words for some legalistic reason because that's what they said in their request, which they say now isn't exactly

what they really meant?
Dr. Tunis: That's a major component of it, but that is the framework under which we have been evaluating this coverage request from the beginning, so we need an answer to that question.
Dr. Holohan: I'm not arguing about it. I'm just trying to make sure that's the reason that question number two is in there.
Dr. Sox: Okay. Now, do you feel confident enough about the state of the evidence to generalize the findings that you can vote, or do you feel like we need to discuss that more? We need a motion. Would somebody wish to move for a vote?
Dr. Redberg: So moved.
Dr. Sox: Second?
Dr. Krist: Second.
Ms. Anderson: So on bullet number two as listed on the screen, we are making a yes or no vote. Those members who wish to vote yes, by a show of hands?

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(No response.)
Ms. Anderson: Those members who wish to vote no?
(Show of hands.)
Ms. Anderson: There are no abstentions and it is a unanimous no. Thank you.
Dr. Sox: Okay. Are there any other motions that members of the panel, voting panel would like to bring in respect to voting question number two? This would be the opportunity if you want to, to make a motion that would extend, it would say that the evidence is adequate to apply the MADIT II trial findings to some subgroup that you feel it does apply to.
Dr. Weil: We still haven't raised the question of whether it applies to the whole group, and that's the first part of the third question. Is the evidence adequate to apply the findings of MADIT II to patients who meet the MADIT II criteria, and then we would, I thought, go on to any additional groups.
Dr. Curtis: Right. We should be discussing bullet three now.
Dr. Lee: I don't think the panel really feels, regardless of the legalities and the specific

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questions, I think most people on the panel want to make a comment about bullet number three.
Dr. Sox: So let's page down to bullet three and let's take a vote on it.
Dr. Curtis: I think what we should do is take out the parentheses there, the stuff that's in there. I mean, it's going to confuse this discussion.
Dr. Sox: Okay.
Dr. Curtis: I think we should just leave it with patients who meet the inclusion criteria, I think that would be better.
Dr. Weil: Could you also say meet inclusion and exclusion too?
Dr. Curtis: I don't have a problem with that.
Dr. Holohan: Dr. Buxton, I thought explained that better than I did, why the exclusion criteria should be there.
Dr. Buxton: I would just go with exactly

as the trial data showed and just say, including the patients who meet the inclusion and exclusion criteria.

Dr. Sox: Yes, Dr. Moss.

Dr. Moss: It seems to me that the first question was the evidence and the second question relates to the application, and the application is on the basis of the evidence, which is on the basis of the inclusion and exclusion criteria.

Dr. Sox: So what's your take on what we ought to do based on that?

Dr. Moss: Well, it's just that the second question is, or the third question is the application, does it apply, does the MADIT II study, which includes the inclusion and exclusion criteria, apply to the Medicare population?

Dr. Redberg: Can I clarify? The exclusion criteria that was printed in the New England Journal trial were eight, including signed consent, and what was sent to us by Guidant included 17 exclusion criteria. Which are we talking about?

Dr. Moss: Let me make just a comment. Anytime you send anything to the New England Journal of Medicine, it gets modified. I think we ought to go by the exclusion criteria that were used in the study. They are very clearly spelled out. The New England Journal modifies and editorializes in a very inappropriate way.

Dr. Redberg: So what was listed --

Dr. Moss: We have the exclusion listed right down here. Do you want me to read them?

Dr. Sox: Dr. Curtis, do you wish to include the things that's in the parentheses or do you think we should delete that?

Dr. Curtis: No. I said please take it out, and it should say, and meet the inclusion and exclusion criteria, that those two modifications should be made to that third bullet, that the inclusion and exclusion criteria.

Dr. Sox: I'm having trouble with this because I don't understand how it differs from the first one that we've already voted on.

Dr. Curtis: Do you have enough evidence, and then you say yes or no. The evidence doesn't say if it's positive or negative or whatever, it just says you have sufficient evidence. This bullet now, is it sufficient to apply it to the Medicare patients.

Dr. Sox: Who meet the inclusion and exclusion criteria, so it's really consistent with our vote on the second one, a yes vote on this would be consistent with our vote on the second one.

Dr. Weil: They're both application questions, obviously, it's just that the subject matter is a little bit different.

Dr. Sox: Okay, I think I got that one through my head. Does everybody understand what we're voting on here? You think you understand the implications of a yes and a no vote? So, I guess it's time for a motion.

Dr. Curtis: I will move the question.

Dr. Matuszewski: Second.

Ms. Anderson: This is a yes or no vote. We're voting on bullet number three as shown on the

slide, and I will ask for the vote. Those voting members who vote yes for the question?

(Show of hands.)

Ms. Anderson: Those voting no on the question?

(No response.)

Ms. Anderson: Okay. No one has abstained. It is a unanimous yes. Thank you.

Dr. Sox: So, the fourth bullet, I just conferred with Dr. Tunis. The fourth bullet, Dr. Tunis doesn't feel we need to vote on, so we can delete that one.

Dr. Weil: Unless the panel simply believes, if it believes that, if it believes that the evidence suggests that the Medicare population would benefit to the same, to approximately the same

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extent as the MADIT II trial results, if the panel wants to consider that.

Dr. Sox: Well, somebody can make a motion about us expressing an opinion about the size of the health effect, but it doesn't sound like it's going to be helpful in setting coverage policy. So if you want to do it, you can. Tom?

Dr. Holohan: I think I may be about to cause more trouble. I don't know that I agreed with Dr. Moss when he said accept all of the exclusion criteria in the protocol, not the ones in the New England Journal of Medicine. I went back to the FDA SSE, and I'm not sure that some of the cardiologists here would agree with some of these exclusion criteria. For example, current use of antiarrhythmic agents, except when indicated for atrial arrhythmias. That would mean a Medicare patient couldn't receive an ICD if they were on Procainamide.

Dr. Buxton: Let me clarify it. Those types of provisions are there because when you're designing a clinical trial, you know --

Dr. Holohan: I understand, and they may be appropriate for designing the clinical trial, but I'm not sure they're appropriate if you're trying to use this as selection criteria for use in Medicare

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patients. There are others. Where the primary care physician refuses. So you have the circumstance where the cardiologist says you need an ICD and the primary care physician refuses to allow it. I mean, it makes sense for a study, but it doesn't make sense for coverage.

Dr. Curtis: These are the ones in the New England Journal article?

Dr. Holohan: No.

Dr. Moss: These are, I would think, judgment questions, to be honest. They are issues that relate to the development of a precise clinical trial. For example, we excluded patients who were involved in another clinical trial. Well, that doesn't apply once you're over the trial. So, I mean, it's --

Dr. Holohan: Okay, but what you're going to face then is a series of Medicare medical carrier directors looking at these exclusion criteria and making decisions as to -- you know, whereas the ones in the New England Journal seem to me limited and very very reasonable. They related to the recency of an acute MI, things that Dr. Buxton talked about.

Dr. Moss: I defer to your judgment on

that.

Dr. Sox: Well, technically we could state the published inclusion and exclusion criteria. Would that do it?

Dr. Redberg: What we voted on was the 17, that was what I asked before we voted, and I assumed the inclusion criteria for the trial was all of those.

Dr. Moss: Within clinical judgment, but I defer to the panel.

Dr. Sox: There were something like seven or eight criteria exclusion criteria in the New England Journal. Does anybody want to pull their, get that one out and we can go over it.

Dr. Holohan: Actually, I don't think there were as many as seven or eight.

Dr. Redberg: There were eight.

Dr. Holohan: Patients were excluded if they had an indication approved by the FDA for an implantable defibrillator were the New York Heart Association functional Class IV, that was the subject of discussion; coronary revascularization within the preceding three months; an MI within the past month; advanced cerebral vascular disease; and then of course, any condition other than cardiac disease associated with a high likelihood of death.

Dr. Sox: That's what I thought we were voting on.

Dr. Holohan: Well, we kind of got stuck with the 17 versus these.

Dr. Sox: Is the panel comfortable with the list that Tom just read and willing to have a statement published that the criteria be inserted to make our point clear on that?

Dr. Tunis: I think the conversation already on the record here is adequate, so I don't think we need to go into this anymore. We don't need to craft the letters of the policy here.

Dr. Sox: Now what about question one, which deals with a coverage issue that you already cover but nonetheless was put before us, how do you want us to deal with that?

Dr. Tunis: I don't think we need to do votes on question number one.

Dr. Sox: So from your point of view, Sean, do we have other business that will help us in our capacity as your advisors?

Dr. Tunis: No.

Dr. Sox: In that case, what do we do to adjourn?

Ms. Anderson: I take over. I have to make a very brief announcement. Please don't leave until I'm finished, thank you.

For continuing information, visit our web site at www.cms.hhs.gov\mcac, or you can go to the CMS web site and click on coverage.

To conclude today's session, would someone move that this meeting be adjourned.

Dr. Holohan: So moved.

Dr. Matuszewski: Second.

Ms. Anderson. Thanks to all.

(Whereupon, the meeting ended at 3:40 p.m.)